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OVARIAN TUMORS IN INFANTS AND IN CHILDREN

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OVARIAN tumors in infants and children are uncommon. Their incidence in girls less than 15 years of age has been stated to be about 1 per cent[1] of all tumors occurring in children of both sexes in this age group.

The purpose of this paper is to determine the clinical symptoms and signs presented by ovarian tumors and their pathologic nature as they occur in infants and children.

HISTORICAL DATA ON GENERAL INCIDENCE

The first ovariotomy on a child for ovarian tumor was performed by Giraldes in 1866. The child was 13 years old.[2] In 1882, Chenoweth[3] reported the case of a girl aged 8 who had a tumor weighing 16½ pounds (7.5 Kg.), which he successfully removed. He collected 23 cases of ovarian tumor in children from the literature. These included operative and nonoperative cases. In 1890, Kelly[4] reported a case in which a multilocular cyst weighing 61 pounds (27.7 Kg.) was removed in 1883 by Dr. Marion Sims, of Tarrytown, N. Y., from a girl 11 years old.

Doran[5] in 1889 reported large bilateral ovarian tumors in a 7 month

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1. Schultz, O. T.: Tumors of Infancy and Childhood, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1926, vol. 8, pp. 707-708.

2. Giraldes, cited by Loeb and Levy.[8g]

3. Chenoweth, W. J.: A Case of Successful Ovariotomy in a Child, Am. J. Obst. **15**:625-628 (July) 1882.

4. Kelly, H. A.: Diseases of Ovaries and Tubes, in Keating, J. M.: Cyclopaedia of the Diseases of Children, Philadelphia, J. B. Lippincott Company, 1890, vol. 3, pp. 731-740.

5. Doran, A.: Large Ovarian Tumours in a Seven Months' Child, Tr. Path. Soc. London **40**:200-208, 1889.

fetus. In 1945 Ziegler[6] reported a case of bilateral ovarian tumors in a 30 week fetus. The pathologic diagnosis was undifferentiated carcinoma.

Bland-Sutton[7] in 1891 collected 60 cases of ovarian tumors in children less than 15 years of age. He classified 46.6 per cent as dermoids, 26.7 per cent as sarcomas and 26.7 per cent as cysts.

From our review of the literature it was evident that data have been reported on more than 200 ovarian tumors in infants and children.[8] Approximately one-third of these growths were simple and multilocular cysts, one-fourth dermoid cysts and more than one-third either carcinoma or sarcoma. The diagnosis of carcinoma or sarcoma of the ovary, often made in the past, has become much less frequent during recent years. The better recognition of granulosa cell tumor and dysgerminoma as pathologic entities during the past fifteen years is probably the reason for this decreasing frequency, and many of the lesions called "sarcoma" and "carcinoma" in the older literature probably were granulosa cell tumors and dysgerminomas. Sarcoma of the ovary is now considered a rare neoplasm.

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6. Ziegler, E. E.: Bilateral Ovarian Carcinoma in a Thirty Week Fetus, Arch. Path. **40**:279-282 (Oct.) 1945.

7. Bland-Sutton, J.: Ovarian Tumors in Infancy and Childhood, in Surgical Diseases of the Ovaries and Fallopian Tubes, Philadelphia, Lea Brothers & Co., 1891, chap. 8, pp. 83-92.

8. (*a*) Bulfamonte, J. C.: Large Ovarian Cyst in Newborn Child, Am. J. Surg. **55**:175-176 (Jan.) 1942. (*b*) Donhauser, J. L.: Malignant Ovarian Tumors in Children, with Report of Case, Albany M. Ann. **27**:20-30 (Jan.) 1906. (*c*) Downes, W. A.: Tumors of the Ovary in Children, J.A.M.A. **76**:443-445 (Feb. 12) 1921. (*d*) Hubert, cited by Taussig, F. J., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 31. (*e*) Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, chap. 33, pp. 385-393. (*f*) Lanman, T. H.: Ovarian Tumors in Childhood with Report of Five Cases, New England J. Med. **201**:555-562 (Sept. 19) 1929. (*g*) Loeb, M. J., and Levy, W.: Ovarian Cysts and Tumors in Children Under Ten Years of Age, with Report of a Case of Teratoid Cyst in a Child Four Years Old Simulating Acute Appendicitis, Arch. Pediat. **49**:651-666 (Oct.) 1932. (*h*) Miller, O. H.: Ovarian Tumors in Childhood, J. Iowa M. Soc. **29**:157-159 (April) 1939. (*i*) Power, D.: Ovarian Cyst Successfully Removed from a Child Aged Four Months, Tr. Path. Soc. London **49**:186-188, 1898. (*j*) Schaeffer, M. H., and Cancelmo, J. J.: Cavernous Hemangioma of Ovary in a Girl Twelve Years of Age, Am. J. Obst. & Gynec. **38**:722-723 (Oct.) 1939. (*k*) Scheffey, L. C.: Sarcoma of the Ovary in Children and Young Girls, Am. J. Obst. & Gynec. **9**:490-502 (April) 1925. (*l*) Schmeisser, H. C., and Anderson, W. A. D.: Ganglioneuroma of the Ovary, J.A.M.A. **111**:2005-2008 (Nov. 26) 1938. (*m*) Sturley, R. F.: Teratomatous Chorionepithelioma of the Ovary: Critical Review of Literature, with Report of New Case, Minnesota Med. **25**:629-637 (Aug.) 1942. (*n*) Wiel, H. I.: A Survey of Ovariotomy at Extremes of Life: Report of a Case in a Girl Aged Five, Bull. Johns Hopkins Hosp. **16**:102-109 (March) 1905. (*o*) Witzberger, C. M., and Agerty, H. A.: Ovarian Tumors in Infancy and Childhood, Arch. Pediat. **54**:339-348 (June) 1937.

MATERIALS AND METHODS

The cases of ovarian tumor in infants and children 14 years of age or younger in which surgical treatment was carried out at the Mayo Clinic during the past twenty-eight years were studied. The history and clinical records in these cases were reviewed, together with the pertinent data relative to symptoms, signs and operative observations. The surgical specimens had been preserved in a 10 per cent solution of "formalin." The gross specimens were examined, and multiple blocks were cut from each specimen. These blocks were transferred to fresh 10 per cent solution of "formalin," sectioned by the freezing method, stained with hematoxylin and eosin and studied histologically. Data were available on 22 cases of ovarian tumor. These cases are classified in the table.

In the discussion of the various types of ovarian cysts encountered at the clinic, we have included pertinent data drawn from the literature in order to present as nearly complete information on this subject as possible.

Ovarian Tumors in Infants and Children Treated at Mayo Clinic in Twenty-Eight Years

	Cases	Per Cent
Simple cyst	7	31.8
Cystadenoma	3	13.7
Teratoma (including dermoid cyst)	10	45.5
Dysgerminoma	1	4.5
Granulosa cell tumor	1	4.5
Total	22	100.0

SIMPLE CYSTS

Incidence.—In Hubert's series[8d] of 175 cases of tumor, 32.5 per cent of the tumors were classified as of simple cysts. In our series of 22 cases 7 tumors were simple cysts, or 31.8 per cent of the entire group.

Age.—Our 7 cases of simple cysts were observed in 4 girls 13 or 14 years old, in 2 children 8 years old and in 1 child 1½ years old. The lone cyst of the lutein variety was in a girl past puberty; the remainder were follicular.

Symptoms and Signs.—Pain was the presenting complaint in 6 cases. It was severe and more or less constant and of less than five days' duration in 4 cases. In the other 2 cases it was slight, recurrent and present over a long period. The pain was located in the right lower quadrant in 2 cases and in both lower quadrants in 1. In 1921, Downes[8c] pointed out that pain, swelling and pressure are frequent symptoms of ovarian cyst. In none of these cases was swelling of the abdomen or a tumor noted by the patient.

Nausea and vomiting occurred in 4 cases. In 3 of these they were associated with sharp pain of short duration and in 1 with recurrent pain

which had been noted for a long period. Mayo and Butsch[9] in 1938 emphasized that pain, together with nausea and vomiting, usually was associated with twisting of the pedicle of the cyst. Diarrhea was present in only 1 case and lasted only one day.

Menstrual irregularities or abnormalities were present in only 1 case. This patient, aged 18 months, who was brought to the clinic because of sexual precocity, had no symptoms referable to the abdomen. Vaginal bleeding, enlarged breasts, presence of pubic hair and increased bone age, as well as a palpable pelvic tumor, were revealed on examination. Examination of the tumor after removal proved it to be a simple cyst. In passing, we wish to mention that this child had no other demonstrable pathologic abnormality and the adrenal glands appeared normal. She recovered from the operation but continued to have symptoms of sexual precocity.

Slight to moderate tenderness in the lower part of the abdomen was found on examination in 5 cases. The tenderness was in the right lower quadrant in 1 case, in the left lower quadrant in 2 cases and in both lower quadrants in 2. A tumor was palpable through the abdominal wall in 1 case and on rectal examination in 4 cases. In 1 case coexisting imperforate hymen and hematocolpos were present.

Complications.—Downes[8c] in 1921 stated that torsion of the pedicle is the commonest complication of ovarian cysts in children. Smith and Butler[10] in the same year collected 25 cases of torsion of the pedicles of ovarian cysts in children and 4 cases of torsion of normal adnexa, which had been reported since 1900. Fowlie[11] stated that 125 cases of twisted ovarian cyst in children have been reported in the past one hundred years. In 5 of our 7 cases of simple cyst the pedicles were twisted, an incidence of 71 per cent.

Diagnosis.—Mayo and Butsch[9] pointed out that the ovarian cyst usually can be felt on abdominal or rectal examination but that it is often confused with abscess. In the cases in which severe pain is present, especially when it is associated with nausea or vomiting due to a twisted pedicle, it may be difficult to differentiate an ovarian cyst from appendicitis or appendical abscess, and an exploratory laparotomy may be required before the diagnosis can be established.

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9. Mayo, C. W., and Butsch, W. L.: Ovarian Tumors Among Young Girls, Minnesota Med. **21**:256-258 (April) 1938.

10. Smith, R. R., and Butler, W. J.: Concerning Torsion of the Uterine Adnexa Occurring Before Puberty, Together with a Consideration of Torsion of Normal Adnexa: Report of a Case and a Review of the Literature Since 1900, Am. J. Obst. & Gynec. **2**:507-521 (Nov.) 1921.

11. Fowlie, J. A.: Twisted Ovarian Cysts in Children, Am. J. Surg. **64**:285-287 (May) 1944.

The preoperative diagnosis was appendicitis in 3 of our cases of simple cyst, appendical abscess in 1, pelvic tumor in 1 and ovarian cyst in 2.

Pathologic Changes.—Simple cysts of the ovary are considered to be retention cysts, not true neoplasms. They are classed as ovarian cysts of follicular type or lutein type according to the cell lining. Cysts of atretic follicles and corpora albicantia also are considered simple cysts. The latter are usualy small and incorsequential.

MacCarty and Sistrunk[12] in 1913 demonstrated that follicular cysts arise from the graafian follicle, and this explanation is generally considered correct. These cysts may be unilocular or multilocular, hemorrhagic or nonhemorrhagic. The multilocular cysts are multiple simple cysts. These cysts are usually small to moderate in size and thin walled and contain clear or blood-tinged clear fluid. Microscopically, the wall is ovarian cortical tissue, and in the small cysts the wall is lined with many layers of granulosa cells. As the cysts grow larger, the lining may be flattened and may be only one, two or three cells thick. In some large cysts the epithelial lining may disappear so that only a fibrous wall is left.

The lutein cysts arise from corpora lutea. They are usually unilocular. Multiple or compound lutein cysts may occur and are usually associated with hydatidiform mole. They are purported to arise from atretic follicles. They may be hemorrhagic or nonhemorrhagic. In the ones without hemorrhage the contents are clear, watery fluid. The cysts are usually small but may be large, with thin walls, the inside of which appears yellow because of the presence of lutein cells. Microscopically, the wall is made up of fibrous tissue and sometimes of atrophic ovarian tissue.

Ewing[13] described different types of lining for lutein cysts: an internal lining of lutein cells, an internal lining of hyaline and laminated tissue with lutein cells underneath and an epithelial lining of a single layer of flat cells with lutein cells or hyaline connective tissue underneath.

Our series included 6 cases of cysts of the follicular type. The smallest cyst was 4 cm. in diameter and the largest 9 cm. All were smoothly lined and thin walled. Two of these 6 cysts were filled with blood clots. Pedicles of both these cysts and of 2 others were twisted. Hematocolpos was associated in 1 case. In 2 of the cases in which twisted pedicles were present, the cysts appeared black and gangrenous, and in 1 of these cases ascites was associated. The other cysts were blue-gray.

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12. MacCarty, W. C., and Sistrunk, W. E.: Benign and Malignant Ovarian Cysts, Surg., Gynec. & Obst. **17**:41-50 (July) 1913.

13. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, chap. 29, pp. 641-671.

Microscopic examination of the cysts of follicular type revealed fibrous ovarian cortical tissue for the most part in the walls. Normal ovarian tissue made up part of the wall in 4 cases. Much hemorrhage was present in the walls of the 4 cysts in which the pedicles had been twisted.

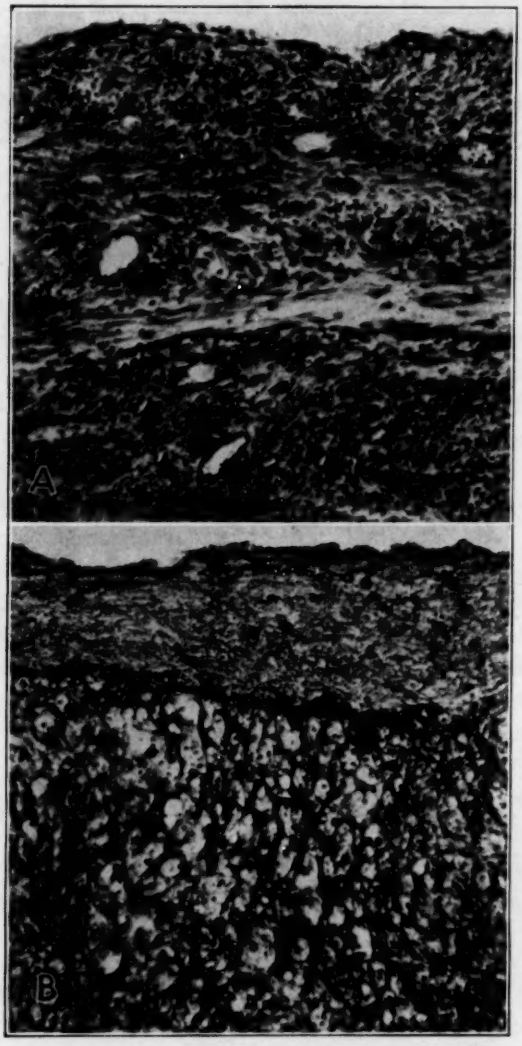

Fig. 1.—Photomicrographs showing, *A*, simple cyst with compressed follicular cell lining, hematoxylin and eosin, × 100, and *B*, simple lutein cyst with lining of lutein cells overlaid with fibrin, hematoxylin and eosin, × 75.

Hematosalpinx also was associated in 3 of these 4 cases, and in 1 of these cases the tube was gangrenous. The lining in 4 of the follicular cysts was made up of compressed and flattened follicular cells, overlying normal-appearing follicular cells (fig. 1). In the other 2 cysts the lining was destroyed by the extensive hemorrhage in the cyst and cyst wall.

The 1 simple cyst of the lutein type was small and unilocular and measured 4 cm. in diameter, with a twisted pedicle. It was smoothly lined and thin walled and was filled with a blood clot. Microscopic examination revealed that the wall was made up of fibrous tissue and compressed ovarian tissue. Hemorrhage was present in the wall. The thick lining of the lutein cells was overlaid by a layer of fibrin (fig. 1*B*).

Treatment.—In uncomplicated cases the treatment of these cysts should be conservative with preservation of as much ovarian tissue as possible. Simple puncture of the small cysts and evacuation of contents are usually sufficient treatment. Most of the larger cysts can be removed and the rest of the ovary preserved. When the pedicle has been twisted and the blood supply interfered with, salpingo-oophorectomy is the procedure indicated.

In 5 of our cases, salpingo-oophorectomy was performed because of interference with the blood supply due to the twisted pedicle. In the other 2 cases the cysts were removed and part of the ovary preserved. There were no deaths resulting from operation and no postoperative complications.

CYSTADENOMA

Incidence.—While cystadenoma is the commonest ovarian neoplasm, according to Geist,[14] its occurrence is uncommon before puberty and rare in children. Cystadenocarcinoma is correspondingly rare in children. In Huber's series[8d] of 175 cases of ovarian tumors in children less than 17 years of age, 10.8 per cent were of cystadenomas. In our series 3 cases of cystadenomas were observed, an incidence of 13.6 per cent.

Age.—In our series these tumors all occurred in girls who had reached the age of puberty. All 3 patients were 14 years old.

Symptoms and Signs.—Swelling or tumor of the abdomen was the presenting complaint in 2 cases of cystadenoma. The duration of the swelling varied from three months to one year. In neither case had there been pain in the abdomen. In the third case the primary complaint was abdominal pain. The pain, which was slight, was in the lower part of the abdomen and was not associated with other symptoms. The pain had occurred daily for more than two years. In 1 of these cases menses previously had been normal, but menstrual flow had not occurred for nine months before admission to the clinic. No menstrual irregularities or associated symptoms were reported in the other 2 cases.

In 1 case pronounced abdominal swelling and distention were noted on examination, but no abdominal tumor could be palpated either through the abdominal wall or on rectal examination. In this case the roentgenogram revealed evidence of healed tuberculosis in the upper

14. Geist, S. H.: Ovarian Tumors, New York, Paul B. Hoeber, Inc., 1942, chap. 5, pp. 154-201.

lobe of the left lung. In the other 2 cases an abdominal mass could be felt. In 1 of these cases the mass could be felt on rectal examination as well.

Diagnosis.—The preoperative diagnosis was ovarian cyst in 1 case, cyst of undetermined origin in 1 and tuberculous peritonitis in 1.

Pathologic Changes.—Cystadenomas usually are divided into two main groups, "serous" and "mucous" cystadenomas.

The serous cystadenomas, which occur a little less frequently than the mucous type, are moderate to large in size and are bilateral in 30 per cent of cases, according to Dockerty.[15] They may be unilocular or multilocular and are filled with thin or thick sticky fluid, which may be brown from admixture with blood. They may exhibit intracystic or extracystic, hard, warty projections.

Microscopically, the simplest unilocular cystadenomas of serous type are lined with a single layer of cuboidal or columnar cells. In the more complex cysts the lining resembles the tubal lining and is made up of columnar cells which often are pear shaped and ciliated.[16] Barzilai[17] described tall, slender intercalary or peg cells and some large, round cells with transparent cytoplasm and dark nuclei. He also described the same changes in the arrangement of these cells in the cyst lining as occur in tubal epithelium. The papillary cords which occur so frequently in the multilocular tumors have the same type of epithelium, with connective tissue cores.

The cystic, nonpapillary types and the hard, warty papillary types are almost always benign. The differentiation of benign from malignant varieties in the other papillary tumors, however, is difficult at times. Novak[16] made the differentiation on the basis of mitoses, stratification of epithelium and invasion of the stroma. He stated, however, that, even in cases of benign papillary cystadenoma, a benign clinical course is not certain. In general, however, when the growth is benign histologically, the clinical course is benign, whereas, when the tumor is histologically malignant, the clinical course is likewise malignant. Novak also stated that most malignant cystadenomas result from malignant degeneration of a previously benign papillary cystadenoma.

The histogenesis of serous cystadenomas is not completely solved. According to most investigators, they arise from the germinal epithelium of the ovary, with subsequent salpingeal differentiation.[18]

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15. Dockerty, M. B.: Ovarian Neoplasms: Collective Review of Recent Literature, Internat. Abstr. Surg. **81**:179-204, 1945; in Surg., Gynec. & Obst., September 1945.

16. Novak, E.: Gynecological and Obstetrical Pathology with Clinical and Endocrine Relations, Philadelphia, W. B. Saunders Company, 1940, chap. 22, pp. 286-299.

17. Barzilai, G.: Atlas of Ovarian Tumors, New York, Grune & Stratton, Inc., 1943, chaps. 10, 12 and 13, pp. 161-176, 203-223 and 223-227.

In our group of cases were 2 of serous cystadenomas. Both tumors were unilocular, thin walled and smoothly lined and filled with thin, watery fluid. One was in the left ovary and the other in the right. Microscopically, their walls were made up of fibrous tissue. One was

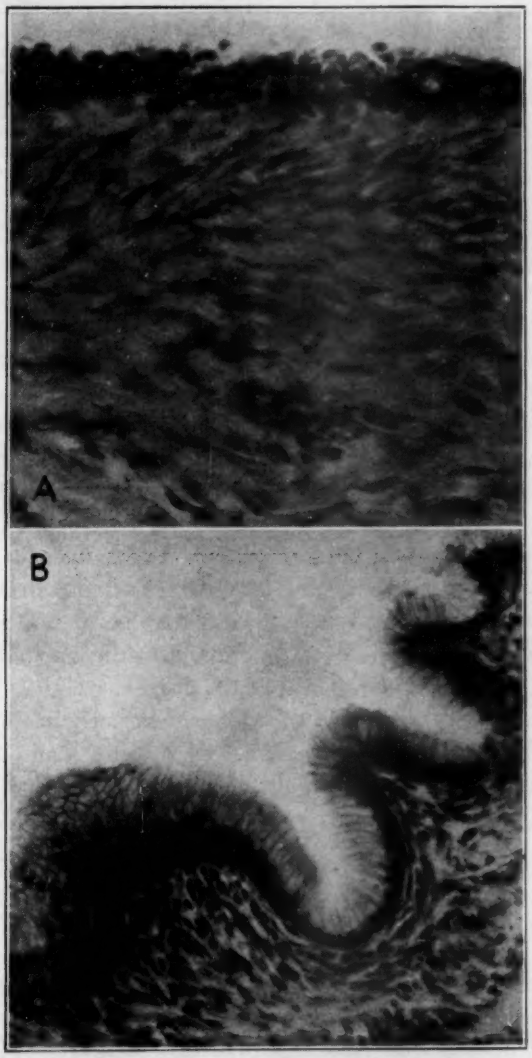

Fig. 2.—Photomicrographs showing, *A*, serous cystadenoma with lining of ciliated, low columnar epithelium, hematoxylin and eosin, × 260, and *B*, mucous cystadenoma with typical lining of columnar cells, hematoxylin and eosin, × 200.

lined with a single layer of low columnar epithelium and the other with ciliated, low columnar epithelium (fig. 2*A*).

18. (*a*) Geist.[14] (*b*) Novak[16] (*c*) Barzilai.[17] (*d*) Schiller, W.: Concepts of a New Classification of Ovarian Tumors, Surg., Gynec. & Obst. **70**:773-782 (April) 1940.

Most mucous cystadenomas are unilateral. Their size usually is moderate to large, but they may be enormous. They may be unilocular or multilocular, and externally they resemble the serous variety. They are filled with a viscid fluid which may be brown from admixture with blood. Schiller[18d] pointed out that this fluid contains true, "old" mucin. Papillary growths occur in only 10 per cent of mucous tumors, but their presence is indicative of malignant changes. In some cases there is a great tendency to proliferation, and the cut surface may show a practically solid tumor or one filled with multiple small, cystic spaces.

Mucous tumors have a characteristic epithelial lining. The cells are tall and columnar, with refractile cytoplasm, dark-staining nuclei close to the basement membrane and many goblet cells. The epithelium is one cell thick. Solid nodules of Brenner tumor are sometimes seen in the wall. Malignant change occurs in approximately 5 per cent of these tumors.[16]

Pseudomyxoma peritonaei is a rare complication of mucous cysts of the ovary. It results from rupture of the cyst with dissemination of its contents over the whole peritoneal cavity. The mucinous content itself may be absorbed, but the cells of the tumor implant themselves on the peritoneum and continue to grow and produce mucin. Any of the abdominal organs may be involved. The condition recurs after operation because it is impossible to remove all the implants. Death usually results from mechanical interference with the peritoneum and the structures within the peritoneal cavity. The condition also may be of appendical origin, and in the surgical treatment of the condition the appendix should be carefully examined as a possible seat of the disease.

Most investigators considered pseudomyxoma peritonaei clinically malignant but histopathologically benign.[18a-c] Woodruff and McDonald,[19] however, considered pseudomyxoma peritonaei of appendical origin to be due to low grade adenocarcinoma of the appendix. Material taken from the peritoneal cavity of a patient with pseudomyxoma peritonaei was injected into mice. The transplant took and produced tumors.[20] Similar transplants by other workers using material from benign mucous cysts failed.

The histogenesis of mucous cysts is not entirely settled. Many writers, including Novak,[16] stated that they arise from overgrowth of entodermal epithelium in a teratoma. Dockerty,[15] in his recent review, summarized the important facts which support this theory. Schiller[18d] proposed the theory that they are müllerian in origin, arise either from müllerian rests or from the germinal epithelium of the ovary and undergo metaplasia.

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19. Woodruff, R., and McDonald, J. R.: Benign and Malignant Cystic Tumors of the Appendix, Surg., Gynec. & Obst. **71**:750-775 (Dec.) 1940.

20. Zondek, B.; Mandl, F.; Sulman, F.; Brezezinski, A., and Tietz, H. G.: Heterotransplantation of Human Pseudomyxoma Peritonei into Mice and Rats, Cancer Research **3**:198-205 (March) 1943.

Barzilai[17] and Ewing[13] favored Schiller's opinion. There is also some evidence that mucous cysts may arise from Brenner tumors.[17]

In our series there was 1 case of mucous cystadenoma. The growth was a large, multilocular, blue-gray tumor of the right ovary which weighed 3.7 Kg. and measured 33 by 21 by 12 cm. The microscopic picture was that of mucous cystadenoma, with typical tall columnar cells, dark-staining nuclei close to the basement membrane and many goblet cells (fig. 2*B*). The stroma was made up of compressed fibrous tissue. Hyalinization and calcification of the stroma were present.

Treatment.—The treatment is surgical removal of the tumor. It is important not to aspirate or rupture these tumors in the course of removal because of the danger of implantation of malignant cells if any should be present.[16] In cases of bilateral tumors some portions of the ovaries should be saved if possible. Radical surgical removal of extracystic lesions is justifiable in malignant examples; even when extensive spread has occurred as much of the lesion as possible should be removed, along with both tubes and ovaries and the uterus, because this procedure will sometimes cure a certain few of these cases. Roentgen or radium therapy should be given after operation in cases in which the lesions are malignant.

Surgical excision of the tumor and salpingo-oophorectomy on the affected side were performed for each of our 3 patients. All the patients recovered without postoperative complications.

TERATOMA

Incidence.—Teratomas are tumors of young persons. In 1916 Seyfarth[21] collected 171 cases of children less than 15 years of age. The dermoid cyst variety of teratoma is more frequent, however, in persons from 20 to 30 years old, according to Barzilai,[22] and relatively rare among children. The embryonal solid type is less frequent than the dermoid cyst variety and appears at an earlier age. In our series of 22 cases of tumors were 10 of teratomas, an incidence of 45.5 per cent. Seven of these 10 tumors were of the dermoid cyst variety. Two were solid teratomas, and 1 was a malignant solid teratoma.

Age.—The distribution as to age was uniform. One patient was less than 5 years of age; 5 were from 5 to 9 years of age, and 4 were from 10 to 15 years old.

Symptoms and Signs.—The chief presenting complaints of the patients who had teratomas were those of abdominal tumor and abdominal pain. Six children complained of abdominal tumors; the duration varied from one day to one year in various cases. In 3 of these cases there was

21. Seyfarth, P. C., cited by Geist,[14] chap. 8, pp. 307-358.

22. Barzilai,[17] chap. 6, pp. 97-129.

some mild, recurring abdominal pain and 1 complaint of frequency of urination. The presenting complaint in the other 4 cases was abdominal pain. In 2 of these cases the pain was mild and recurrent and was localized in the right lower quadrant; there were no other symptoms. The pain had been present for six weeks in 1 case and for one year in the other. In the other 2 cases the pain had been present four days and seven weeks, respectively. Nausea and vomiting had been present on one occasion in each case.

A mass was felt through the abdominal wall in 6 cases and in 2 of these 6 cases on rectal examination also. In the other 4 cases the tumor was palpated on rectal examination. These masses were the only physical signs.

The diagnosis of dermoid cyst often may be made before operation from evidence obtained in a roentgenogram of the abdomen. Teeth and calcification are recognizable in roentgenograms in 41 per cent of cases of dermoid cyst.[23] The presence of what has been called the "Robins and White sign" has received attention from radiologists during recent years.[24] This sign is the appearance on the roentgenogram of an ovoid mass of diminished density, encircled by a well defined ring of increased density, delineating the mass from the surrounding soft tissues. Good[23] reported this sign present in from 25 to 40 per cent of cases of dermoid cysts.

In 3 of the cases in our series the presence of a pelvic tumor was evident on the roentgenograms, and, in 2 of these cases, enough calcification was present to allow the roentgenographic diagnosis of dermoid cyst. The Robins and White sign was not observed in any of our cases.

Complications.—One of the important clinical aspects of teratomas and dermoid cysts is the frequency with which they twist on their pedicles and produce acute conditions within the abdomen. In 1921, Smith and Butler[10] collected 25 cases of torsion of ovarian cysts in children, 60 per cent of which were dermoid cysts. In 1928, Kincaid and Andrews[25] collected 5 cases of twisted ovarian cysts in children less than 5 years of age and reported their own case, that of a girl 5 years old who had an acute abdominal condition produced by a twisted dermoid cyst. Marshall[26] reported that 12 per cent of dermoid cysts had twisted pedicles.

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23. Good, C. A.: The Roentgenologic Diagnosis of Dermoid Cyst of the Ovary, Proc. Staff Meet., Mayo Clin. **15**:265-266 (April 24) 1940.

24. Danelius, G.: A Neglected Sign for Roentgenologic Diagnosis of Intra-Abdominal Dermoid Cyst, Am. J. Obst. & Gynec. **38**:348-350 (Aug.) 1939. Robins, S. A., and White, G.: Roentgen Diagnosis of Dermoid Cysts of the Ovary in the Absence of Calcification, Am. J. Roentgenol. **43**:30-34 (Jan.) 1940. Good.[23]

25. Kincaid, H. L., and Andrews, E.: Twisted Ovarian Cyst in Five Year Old Child, Am. J. Obst. & Gynec. **15**:207-212 (Feb.) 1928.

26. Marshall, J. M.: The Diagnosis of a Dermoid Cyst of the Ovary, Proc. Staff Meet., Mayo Clin. **3**:4-5 (Jan. 4) 1928.

Loeb and Levy[8g] pointed out the difficulty of distinguishing acute appendicitis from teratoma with a twisted pedicle.

Occasionally, a dermoid cyst will rupture and cause severe peritonitis because of the irritating nature of the contents of the cyst. Piper[27] in 1941 reported 2 cases of rupture of dermoid cysts due to trauma.

In 2 of our 10 cases of teratoma, twisted pedicles were present. In both cases pain was the outstanding symptom and in 1 it was accompanied with nausea and vomiting.

Diagnosis.—Two tumors were diagnosed correctly as dermoid cysts by means of roentgenograms of the abdomen. In 1 case the preoperative diagnosis was appendical abscess and in the other case it was pelvic tumor.

Pathologic Changes.—The dermoid cyst and solid teratoma represent adult and embryonal types of the same growth.[28] The dermoid cyst is a cystic tumor and the teratoma a solid one. The dermoid cyst most frequently is made up of overgrowth of one type of tissue, usually skin, with hair follicles, sebaceous glands and sweat glands. In recent years, however, investigators discovered that careful search will reveal the presence of the three germinal layers in the majority of dermoid cysts if not in all of them.[29]

Small to large dermoid cysts occur and they are usually smooth and lobulated on the outside. They are bilateral in 12 per cent of cases.[15] These cystic tumors are filled with sebaceous material and hair. Teeth, cartilage and bone may be grossly evident. Often there is a raised area on the wall of what appears grossly otherwise as a simple cyst. Hair usually is growing from this area, and microscopically other structures characteristic of a dermoid cyst may be evident. If sections from these tumors are studied carefully under the microscope, ectodermal and mesodermal derivatives will be seen in practically all such growths, and entodermal derivatives will be observed in considerably more than 50 per cent of the cases.[29]

Dermoid cysts are usually benign tumors, but secondary malignant lesions may occur. Barzilai[22] stated that the incidence of secondary malignant growth in dermoids is about 3 per cent. Epidermoid carcinoma is the commonest secondary malignant lesion.

The embryonic teratoma is a solid tumor, although small cystic spaces may be present in it. The tumor may be small or of moderate size. Sometimes its capsule ruptures, and it spreads to involve neighboring organs. The teratoma is made up of tissues representing all three germinal lay-

27. Piper, M. C.: Traumatic Rupture of Dermoid Cyst of Ovary, Proc. Staff Meet., Mayo Clin. **16**:349-352 (May 28) 1941.

28. Ewing,[13] chap. 30, pp. 672-683.

29. Blackwell, W. J.; Dockerty, M. B.; Masson, J. C., and Mussey, R. D.: Dermoid Cysts of the Ovary: Their Clinical and Pathologic Significance, Am. J. Obst. & Gynec. **51**:151-172 (Feb.) 1946.

ers, and all sorts of tissues have been observed in tumors of this type. Some of these tissue elements can be recognized easily on histologic examination, but other elements may be atypical and unidentifiable. Embryonic tissues are commonly seen. An overgrowth of some type of tissue, such as thyroid, may produce the so-called struma ovarii.

The embryonic teratomas are all potentially malignant, and they should be studied carefully before being termed "benign." Smeltzer[30] recorded that of 32 young girls who had teratomas, 65 per cent died of their disease. Sturley[8m] reported 8 cases of teratomatous chorioepithelioma (chorionic carcinoma, chorioma) in children before puberty.

The histogenesis of teratomas is not settled. Various hypotheses have been formulated which suggest that they arise from isolated blastomeres or early mesenchyma or are due to parthenogenesis.

In our series there were 7 cases of the dermoid cyst variety of teratoma. None of the tumors were bilateral. They occurred on the left side in 4 cases and on the right in 3. The largest weighed 800 Gm. and measured 15 by 12 by 11 cm., and the smallest weighed 28 Gm. and measured 5 by 4 by 4 cm. All the tumors except 2 were unilocular and contained varying amounts of hair and white, greasy material. In 2 unilocular cysts hair was growing from a small, raised area in one part of the wall. In 2 cases the pedicles were twisted. In no instance had the wall of the cyst ruptured. The cysts appeared gray from the outside.

Sections of various parts of the wall of each cyst were studied microscopically. Ectodermal and mesodermal derivatives and ovarian tissue were observed in all cases and entodermal derivatives in 3 cases. The last were represented by gastrointestinal epithelium, salivary gland epithelium of the respiratory tract and thyroid tissue. Hemorrhage was present in 3 cysts, in 2 of which the pedicles were twisted.

Three teratomas in our series were of the solid embryonic types. Two occurred in the right ovary and one in the left. All were blue-gray and lobulated; they had smooth capsules and were not attached to the pelvic wall or to other organs. The largest growth weighed 1,135 Gm. and measured 9 by 15 by 8 cm.; the smallest weighed 750 Gm. and measured 15 cm. in diameter. The cut sections revealed small cystic spaces. The cut surfaces were gray with yellow streaks. None of the pedicles of the embryonal teratomas were twisted.

Numerous blocks were cut from various parts of the tumors and studied microscopically. In 2 of the tumors, the microscopic pictures were similar. In both these cases ectodermal derivatives predominated. Much immature brain tissue, smooth and striated muscle, fat and lymphocytes were present. Sections of embryonic retina were observed in 1 tumor and embryonic teeth in the other. An abundance of immature

30. Smeltzer, M.: Solid Teratoma of the Ovary in the Young Girl, Am. J. Obst. & Gynec. **41**:616-623 (April) 1941.

and mature cartilage and bone, gastrointestinal epithelium, salivary gland and epithelium similar to that in the respiratory tract, with underlying mucous glands, was present in both tumors. In 1 tumor an embryonic thyroid gland and pancreatic tissue were observed. There was hemorrhage with areas of necrosis in 1 tumor and a small abscess in the other. No definite evidence of a malignant change was present in either tumor.

The third tumor was made up for the most part of diffuse adenocarcinoma. Squamous cell epithelium and cartilage were present in some areas, but the rest of the tumor consisted of a stroma of young connective tissue, with malignant cells scattered throughout. The cells were small, with round or oval, dark-staining nuclei with large, prominent nucleoli and frequent mitotic figures. These cells seemed to attempt to form glands in some areas, but in others they were in groups with no particular arrangement. The stroma was hyalinized in some areas. A diagnosis of embryonic adenocarcinoma in a teratoma was made.

Treatment.—The treatment for dermoid cysts is surgical removal. Often the tumor is so large that the ovary is destroyed and removed with the tumor. Small dermoid cysts usually can be shelled out of the involved ovary and the ovary preserved. The cyst should be removed without rupturing if possible, because the contents are irritating to the peritoneum.

Salpingo-oophorectomy on the involved side was performed in 5 of our cases of dermoid cysts, and simple removal of the cyst and involved ovary was done in 2 cases. Each of the patients made an uneventful recovery from the operation.

The embryonic varieties of teratoma are all potentially malignant, and the safest treatment is radical surgical removal followed by roentgen therapy. It is desirable to preserve the uterus and some ovarian function if possible in children, and, if the tumor is well encapsulated and not attached to surrounding tissues, simple removal of the tumor and involved ovary may be indicated, unless immediate microscopic examination of frozen sections reveals an obviously malignant growth. It must be remembered, however, that to prove a teratoma malignant may require study of many sections and that, although immediate study of frozen sections may show malignant growth, failure to discover malignant cells in one or more frozen sections does not necessarily mean that the tumor is benign. Patients treated conservatively should be examined carefully at frequent intervals following the operation, and the possibility of recurrence should always be kept in mind.

In our series in the 2 cases of embryonic teratomas in which no malignant change was demonstrable, treatment consisted of removal of the tumor and salpingo-oophorectomy in 1 case and of panhysterectomy in the other. In the latter case three courses of roentgen therapy were given after the operation. The postoperative period for both patients was

uneventful, and both were living and well twelve and nine years, respectively, after operation.

The malignant teratoma was treated by removal of the tumor and salpingo-oophorectomy. In this case radium treatment was carried out after operation. The patient recovered uneventfully from the operation but died four months later from recurrence of the tumor.

DYSGERMINOMA

Incidence.—In 1931, Meyer[31] described this tumor, which corresponds to the seminoma in men, and named it "dysgerminoma." Previous to his report these tumors had gone unrecognized. Many of the tumors called "carcinoma" and "sarcoma" in the older literature probably were dysgerminomas. About 200 cases of dysgerminoma have been reported in the literature.[15]

Age.—Dysgerminomas usually occur in patients who are in the second or third decade of life; this age incidence is in contrast to that of seminoma, which usually occurs among patients who are ten or more years older. Barzilai[32] stated that approximately one third of the published cases of ovarian dysgerminomas had occurred in children. Eleven of Meyer's patients were between 9 and 18 years of age. Six of Fauvet's[33] 36 patients were children between the ages of 9 and 13 years, and Novak and Gray[34] reported 4 cases of children less than 16 years of age. In our series of 22 cases of ovarian tumor among children, dysgerminoma was present in 1 case, an incidence of 4.5 per cent.

Symptoms and Signs.—Dysgerminomas in the early stages produce the same symptoms as other pelvic tumors, namely, abdominal swelling, pain and symptoms of pressure on the bladder and rectum. The more malignant forms invade surrounding organs and produce more serious disturbances. They also may produce symptoms in distant organs from metastasis. Ascites frequently occurs and produces pronounced abdominal swelling.

Dysgerminomas often occur in persons with pseudohermaphroditism and are frequently seen in patients with genital hypoplasia.

Pathologic Changes.—The dysgerminomas are solid tumors which frequently contain areas of hemorrhage or necrosis. They may be small or large, unilateral or bilateral. The capsule may be intact, and when it is the tumor has a rubbery consistency and usually is unattached to

31. Meyer, R.: The Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characteristics, Am. J. Obst. & Gynec. **22**:697-713 (Nov.) 1931.

32. Barzilai,[17] chap. 5, pp. 77-97.

33. Fauvet, E.: Ueber das grosszellige solide Karzinom der Keimdrüsen (Disgerminom-Robert Meyer), Zentralbl. f. Gynäk **58**:2162-2170 (Sept. 15) 1934.

34. Novak, E., and Gray, L. A.: Disgerminoma of the Ovary, Am. J. Obst. & Gynec. **35**:925-937 (June) 1938.

other organs. In other cases the tumor infiltrates and invades the surrounding organs, and distant metastases may occur. Ascites is commonly present.

The microscopic picture is identical with that of the seminoma in the male patient and presents a well known picture. The cells are large, round or oval with large hyperchromatic nuclei. They may be arranged in alveoli, strands or an indifferent pattern. There is a small amount of fibrous tissue stroma, with extreme infiltration of lymphocytes. Giant cells are not uncommon. All types are highly malignant.

Most writers accept Meyer's[31] hypothesis that these tumors arise from cells present in gonads of both male and female infants before the stage of sexual differentiation. The facts supporting this hypothesis were recently summarized by Dockerty.[15]

The dysgerminoma is a malignant tumor microscopically, but the degree of its malignancy is variable. Schiller[35] in 1936 stated that these tumors can be cured by operation in 70 to 90 per cent of cases of young girls. Meigs[36] reported only 1 fatality in 12 cases of dysgerminoma and so considered the growth of low grade malignancy. Geist[37] considered it a highly malignant tumor with frequent metastasis and recurrence. Kirshbaum and Newman[38] supported this view.

Treatment.—Since dysgerminomas are radiosensitive, the safest treatment is radical removal followed by roentgen therapy. If the tumor is unilateral and well encapsulated, surgical removal with preservation of the other ovary and the uterus may be justified. The patient, however, must be watched carefully for signs of recurrence, because the lesion is bilateral in 33 per cent of cases and the so-called normal contralateral ovary may harbor an incipient neoplasm at the time of operation.

REPORT OF A CASE

CASE 1.—The patient, a white girl 12 years old, came to the clinic because of a tumor of the abdomen. Family history and past history were noncontributory. Eight days before her admission she complained of pain in the lower part of the back. On examination her family physician discovered a mass in the abdomen. The pain shifted to the lower part of the abdomen, and the mass increased in size. She also complained of loss of energy and appetite and of tiring easily.

When the child was examined at the clinic, a large mass was palpable in the abdomen to the left of the midline and another to the right of the midline. One mass was palpable on rectal examination also. The preoperative diagnosis was bilateral ovarian sarcoma.

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35. Schiller, W.: Recent Findings in Solid Ovarian Tumours, J. Obst. & Gynaec. Brit. Emp. **43**:1135-1144 (Dec.) 1936.

36. Meigs, J. V.: Medical Progress: Gynecology; Neoplasms of the Ovary, New England J. Med. **228**:52-60 (Jan. 14) 1943.

37. Geist,[14] chap. 7, pp. 254-306.

38. Kirshbaum, J. D., and Newman, B.: Malignant Dysgerminoma of the Ovary, Am. J. Obst. & Gynec. **45**:337-340 (Feb.) 1943.

Bilateral ovarian tumors were removed, and bilateral salpingectomy was performed. One growth was attached to the surrounding structures, but the surgeon removed all the gross tumor.

The tumors were large, solid and encapsulated. They were gray and weighed 1,370 Gm. together. One measured 17 by 10 cm. and the other 12 by 9 cm. The cut sections showed them to be soft but solid throughout, with no particular markings.

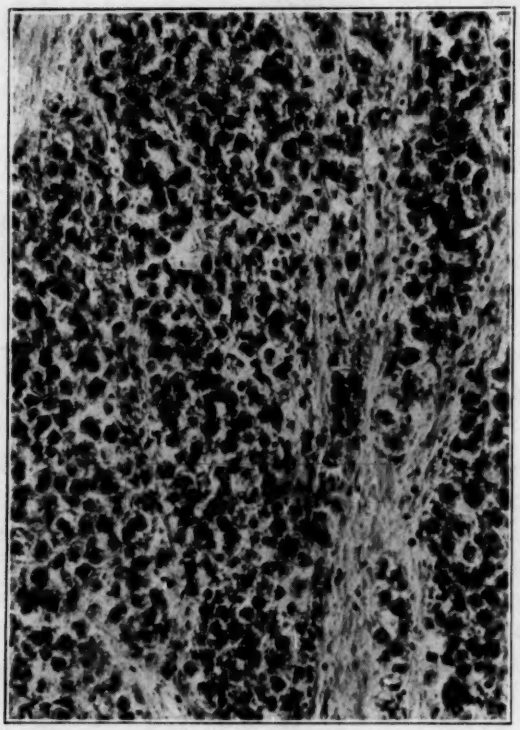

Fig. 3 (case 1).—Dysgerminoma of the ovary showing indifferent pattern, hematoxylin and eosin; × 165.

Microscopic examination revealed the characteristic large, round cells with dark-stained nuclei of the dysgerminoma (fig. 3) and many mitotic figures. Abundant connective tissue which was infiltrated with lymphocytes separated the tumor cells into small groups and formed the so-called alveolar pattern. In a few areas the tumor cells formed a diffuse pattern with little connective tissue. In some areas necrosis and degeneration of cells were beginning.

The patient made an uneventful recovery from the operation and was given roentgen therapy. The tumor recurred, however, and she died three months later.

GRANULOSA CELL TUMOR

It is only during the past fifteen years that the occurrence of granulosa cell tumor has been properly recognized in children. The occurrence of sexual precocity in cases of ovarian tumor had been known for many years, and in most cases a diagnosis of carcinoma or sarcoma of the ovary had been made. Since granulosa cell tumor is by far the common-

est ovarian tumor which causes sexual precocity in children, it is probable that many of the ovarian lesions reported as carcinoma or sarcoma were granulosa cell tumors.

Incidence.—In 1931, Meyer[31] reported on 33 cases of granulosa cell tumor, 3 of which were of children. In these 3 cases precocious development, uterine bleeding and hypertrophied breasts were noted.

Novak[39] in 1933 observed that, of approximately 200 cases of sexual precocity reported in the literature, in only the 3 cases published by Meyer[31] in 1931 was the etiologic role of granulosa cell tumor clearly established. Novak reported 3 cases of his own, including 1 which had been reported by Wiel[8n] in 1905 as of adenocarcinoma.

In the available literature on granulosa cell tumor, Bland and Goldstein[40] in 1935 found 12 cases of granulosa cell tumor in children less than 15 years of age. Sexual precocity occurred in all cases. Parks[41] in 1938 found only 8 cases of granulosa cell tumor in children less than 10 years of age. He reported his own case of a girl 5 years old. Lull[42] in 1941 reviewed the literature and found 16 cases of granulosa cell tumor reported in children. He added 2 cases of his own, 1 of a child 9 months old, one of the youngest in whom the condition had ever been reported. Talbot and Talbot[43] in 1945 stated that more than 20 cases of granulosa cell tumor in children less than 14 years of age have been reported.

In our series of 22 cases of ovarian tumors in children 14 years of age and younger, there was 1 of granulosa cell tumor, an incidence of 4.5 per cent.

Age.—Granulosa cell tumors occur at any age in childhood. Zemke and Herrell[44] in 1941 reported a case of granulosa cell tumor in a child 14 weeks old. This child is the youngest in whom granulosa cell tumor has been reported. The tumor was successfully removed, and the child was well three years later.

Symptoms and Signs.—The granulosa cell tumor produces an estrogenic substance, thus causing symptoms and signs of sexual precocity in

39. Novak, E.: Granulosa Cell Ovarian Tumors as a Cause of Precocious Puberty with a Report of Three Cases, Am. J. Obst. & Gynec. **26**:505-519 (Oct.) 1933.

40. Bland, P. B., and Goldstein, L.: Granulosa and Brenner Tumors of the Ovary, Surg., Gynec. & Obst. **61**:250-266 (Aug.) 1935.

41. Parks, J.: Granulosa Cell Tumors of the Ovary with Precocious Puberty, Am. J. Obst. & Gynec. **36**:674-679 (Oct.) 1938.

42. Lull, C. B.: Pubertas Praecox Due to Ovarian Tumors, Am. J. Obst. & Gynec. **41**:445-453 (March) 1941.

43. Talbot, F. B., and Talbot, N. B.: Pituitary and Suprarenal Glands, Gonads, Pineal Body, Sex Precocity, Obesity, and Progeria, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 1, chap. 40, pp. 1-35.

44. Zemke, E. E., and Herrell, W. E.: Bilateral Granulosa Cell Tumors, Am. J. Obst. & Gynec. **41**:704-707 (April) 1941.

children. Vaginal bleeding, enlargement of breasts, appearance of pubic hair and premature development of the external genitalia occur. The uterus is enlarged, and varying amounts of precocious growth and psychologic development may be associated.

The vaginal bleeding is anovulatory bleeding, not a true cyclic menstruation, owing to variation in the amount of estrogenic substance in the blood stream. Estrogens are excreted in amounts greater than normal for a nonpregnant adult woman. The excretion of estrogens decreases after removal of the tumor.

In addition, the granulosa cell tumor may produce the symptoms and signs associated with any pelvic tumor. These signs are enlargement of the abdomen, symptoms from pressure on the rectum and bladder and abdominal pain. In the malignant variety symptoms may be produced from invasion of surrounding structures or metastasis.

Differential Diagnosis of Sexual Precocity in Females.—At this point it seems well to consider in some detail the differential diagnosis of sexual precocity before the presentation of the remainder of the material on granulosa cell tumor. Puberty may be defined as the age at which the ability to procreate becomes established. For girls this occurs at some time between 10 to 16½ years of age. The average age is 13 years. Puberty is characterized by ovulation and the onset of cyclic menstruation. In some girls menstruation may be anovulatory in type for a while. The period of adolescence which leads up to puberty is characterized by the appearance and development of sex characteristics. In girls this period includes growth of the bony pelvis, development of breasts, appearance of pubic and axillary hair, growth of genitalia, acne and deepening of the voice. During this time excretion of estrogens rises rapidly, and, whereas the normal, daily excretion of estrogens in the first eight years of life is from 0 to 10 international units, during adolescence and adult womanhood it ranges from 0 to 1,000 international units.[43] Follicle-stimulating gonadotropic hormone also appears in the urine of girls after they reach the age of 11 years.[45] While young girls secrete small amounts of androgen as measured by excretion of 17-ketosteroids, normal girls who are past the age of 12 years should excrete at least 1 mg. of 17-ketosteroids daily, and at the age of 18 years they should be excreting 7 to 8 mg. daily.[46]

The excretion of sex hormone by the maturing ovary causes the development of the other sex organs and of the secondary sex characteristics. The maturing of the ovaries, in turn, depends on the secretion of the gonadotropic hormones by the pituitary body. What causes the

45. Nathanson, I. T.; Towne, L. E., and Aub, J. C.: Normal Excretion of Sex Hormones in Childhood, Endocrinology **28**:851-865 (June) 1941.

46. Talbot, N. B.; Butler, A. M.; Berman, R. A.; Rodriguez, P. M., and MacLachlan, E. A.: Excretion of 17-Keto Steroids by Normal and by Abnormal Children, Am. J. Dis. Child. **65**:364-375 (March) 1943.

pituitary to start the secretion of gonadotropic hormones, thus bringing about puberty, is not exactly known. It is considered that the maturing hypothalamus in some way or other affects the pituitary body.

Sexual precocity may be defined as the development of the genitalia and secondary sex characteristics approaching adult proportions during the first eight to ten years of life. In girls it is caused by abnormal excessive secretion of estrogenic substance. Estrogen is usually secreted in an amount much greater than that secreted by normal adults.

"Precocious puberty" is the term used when the ability to procreate is established in children. In this condition in the female child, secretion of gonadotropic hormone by the pituitary gland causes maturation of the ovaries and brings about all the features of puberty before the normal time. The amount of estrogen excreted is usually less than or equal to that excreted by a normal adult.[47] The conditions which cause the pituitary to begin this secretion will be discussed later.

About 600 cases of sexual precocity in female children, including cases of virilization in young girls, due to adrenal tumor, have been recorded in the literature.[47a] The idiopathic or constitutional type of sexual precocity is the commonest.[48] In this type true precocious puberty occurs within the first eight years of life. No etiologic agent or organic lesion can be discovered in these patients. The symptoms and signs are those of puberty in a young female child. Studies to determine the presence of gonadotropins give negative results, although gonadotropins theoretically should be present. These results are probably due to inadequate methods for determining these values. The amount of estrogen excreted is less than or equal to that of a normal woman.[43] In these cases the ovaries mature, ovulation occurs and corpora lutea are formed. These changes can be demonstrated on biopsy of the ovary if laparotomy should be undertaken.[48a] If a biopsy specimen of the endometrium is taken at the end of the menstrual cycle, secretory endometrium should be obtained. These patients usually become undersized adults because of early closure of epiphyses. Precocious pregnancy can occur, and many cases have been reported.[49] The absence of a palpable pelvic tumor when these signs of precocious puberty are present should enable one to differentiate true precocious puberty from granulosa cell tumor. Precocious puberty is much commoner than granulosa cell tumor, but it is the condition most likely to be confused with that resulting from the tumor. The differential diagnosis in most cases should be made without lapar-

47. (*a*) Seckel, H. P. G.: Precocious Sexual Development in Children, M. Clin. North America **30**:183-209 (Jan.) 1946. (*b*) Talbot and Talbot.[43]

48. (*a*) Novak, E.: The Constitutional Type of Female Precocious Puberty with a Report of Nine Cases, Am. J. Obst. & Gynec. **47**:20-42 (Jan.) 1944. (*b*) Seckel.[47a]

49. Reuben, M. S., and Manning, G. R.: Precocious Puberty, Arch. Pediat. **39**:769-785 (Dec.) 1922.

otomy, but, if laparotomy is performed, biopsy of the ovaries should establish the diagnosis.

Our case of simple cyst with precocious puberty was, we believe, an example of idiopathic precocious puberty. We cannot give further details or be more specific because we have not been able to reexamine this patient.

Another type of precocious puberty in children is the cerebral or intracranial type. It is rare in female children, for only about 9 cases have been recorded.[47a] This type is due to an organic lesion in the region of the midbrain or the hypothalamus. Four cases of verified tumor of the midbrain have been reported.[50] Among the tumors were a hamartoma,[51] a hyperplastic abnormal tuber cinereum[52] and a cyst of the third ventricle.[50] Other causes were hydrocephalus and encephalitis.[53] Pineal tumors are known to cause precocious puberty in boys, but no instance of precocious puberty caused by pineal tumor has been reported in a girl.

The mechanism by which hypothalamic tumors cause precocious puberty is not known. The opinion has been expressed that in some way or other through nerve stimulation the pituitary causes the production of gonadotropic hormones, which stimulates the ovaries to mature and produces all the changes which occur with the onset of puberty.

The symptoms and signs and laboratory findings in cases of hypothalamic tumors are those of idiopathic or constitutional precocious puberty. In addition, however, neurologic signs are usually present, although they may be late in arising. The occurrence of choked disks, paralysis of the ocular muscles, unequal pupils or convulsions calls attention to the cerebral nature of the lesion. Other symptoms and signs of hypothalamic disturbance, such as polydipsia, polyuria, polyphagia, obesity or disturbance of sleep may be present. Roentgenologic examination of the skull and air encephalograms may reveal displacement of the pineal body or other structures, hydrocephalus or ventricular block. The neurologic signs may be late in arising, however, and these cases may be classed as of the constitutional type at first. The condition may be separated from granulosa cell tumor by the same criteria that the consti-

50. Flicker, D. J.: Pubertas Praecox in a Female Infant Caused by Ventricular Cyst, J. Nerv. & Ment. Dis. **98**:42-47 (July) 1943.

51. Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood, Am. J. Dis. Child. **59**:579-628 (March) 1940.

52. Bronstein, I. P.; Luhan, J. A., and Mavrelis, W. B.: Sexual Precocity Associated with Hyperplastic Abnormality of the Tuber Cinereum, Am. J. Dis. Child. **64**:211-220 (Aug.) 1942.

53. Dorff, G. B., and Shapiro, L. M.: A Clinicopathologic Study of Sexual Precocitv with Hydrocephalus, Am. J. Dis. Child. **53**:481-499 (Feb.) 1937. Ford, F. R., and Guild, H.: Precocious Puberty Following Measles Encephalomyelitis and Epidemic Encephalitis, with Discussion of Relation of Intracranial Tumors and Inflammatory Processes to Syndrome of Macrogenitosomia Praecox, Bull. Johns Hopkins Hosp. **60**:192-203 (March) 1937.

tutional type is, namely, the occurrence of true precocious puberty and the absence of pelvic tumor. The appearance of neurologic or hypothalamic symptoms and signs eventually will make the diagnosis certain.

Another cause of precocious puberty in female children is osteitis fibrosa cystica (Albright's disease or polyostotic fibrous dysplasia of bone with cutaneous pigmentation). Albright and his associates[54] called attention to this disease in 1937. More than 25 cases of this disease with all features of the syndrome have been reported in female children.[47a] If the cases in which one or more of the features are missing are included, many more cases of this disease probably have occurred. The cause is unknown, but primary disturbance of the central nervous system or congenital developmental defects have been suggested.[54] The complete syndrome has three main characteristics: 1. Bony lesions are present which resemble cysts in the roentgenogram but which prove to be osteitis fibrosa on microscopic examination. There is a tendency for the cysts to be unilateral. Fractures due to the weakening of the bone and deformities from malalined healing are often present. 2. Brown pigmented areas appear, usually on the same side as the bony lesions. 3. Precocious puberty is present in female children. Laboratory studies reveal nothing abnormal except an increased value for phosphatase. The differentiation of this syndrome from granulosa cell tumor is based on the presence of the pigmentation and bone cysts and the absence of a pelvic tumor.

Sexual precocity in the female child, as opposed to precocious puberty, is caused by primary endocrine lesions. These occur in the adrenal glands and ovaries. No case of sexual precocity in association with a pituitary tumor has ever been reported.

About 75 cases have been reported in which sexual precocity in female children was caused by hyperplasia, adenoma or carcinoma of the adrenal cortex.[47a] In most cases, however, the growths caused symptoms and signs of virilization or pituitary basophilism (Cushing's disease). According to Seckel,[47a] adrenal cortical lesions rarely cause feminization, and only about 7 cases have been reported.

In the cases of feminization, symptoms and signs of sexual precocity occur, which are caused by the secretion of estrogens by the tumor. The amount of excretion is usually much more than that of normal adults. The ovaries are immature; ovulation does not take place, and the endometrium does not reach the secretory phase.

Greatly increased excretion of androgen and signs of virilization of varying degrees may be present. The signs are an enlarged clitoris, a deep voice, acne and hirsutism of the face, arms and legs. Some of the symptoms and signs of pituitary basophilism also may be present. These

54. Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females: Report of Five Cases, New England J. Med. **216**:727-746 (April 29) 1937.

are obesity, hypertension, osteoporosis, mottling and striae of the skin, polycythemia and a tendency toward diabetes. If the tumor is present during fetal life, pseudohermaphroditism also may be associated with it. Sometimes the tumor of the adrenal gland may be palpable. If it is a carcinoma, signs of distant metastasis may be present. A roentgenogram of the abdomen or pyelograms may reveal a tumor above the kidney. In some instances tumors were shown on roentgenograms after injection of air about the adrenal gland. The presence of a tumor, as determined by any of these methods, together with the signs of virilization or of pituitary basophilism which may be present in the absence of an ovarian tumor, enables the differentiation of granulosa cell tumor from a lesion of the adrenal cortex. The increased excretion of androgen, as measured by the amount of 17-ketosteroids in the urine, is characteristic of adrenal tumor and is absent in cases of granulosa cell tumor.

The lesions in the ovary which may cause sexual precocity are granulosa cell tumor and teratomatous chorioepithelioma. About 30 verified cases of granulosa cell tumor in children have been reported.[47a] Granulosa cell tumors account for only about 5 per cent of the sexual precocity in female children. If the 30 unverified cases which may have been of granulosa cell tumor[47a] are considered, the incidence of sexual precocity in female children which is caused by granulosa cell tumor is at the most about 10 per cent. This low incidence is important to remember when one is confronted with cases of sexual precocity in a female child.[48a]

Since the symptoms and signs of granulosa cell tumor are those of sexual precocity, it is well to keep in mind that in children who have granulosa cell tumors true precocious puberty does not occur and cyclic menses and secretory endometrium are not present. The excretion of estrogen is much greater than that of a normal woman. The tumor may be palpable on rectal examination.

The other ovarian tumor which could be confused with granulosa cell tumor is the rare teratomatous chorioepithelioma. Eight cases of sexual precocity caused by teratomatous chorioepithelioma have been recorded in the literature, according to Sturley.[8m] Patients with growths of this type present all the signs and symptoms of sexual precocity, with a palpable pelvic tumor, that patients who have granulosa cell tumor present. In the presence of a teratomatous chorioepithelioma, however, there is a greater chance of metastasis being present, and results of the Aschheim-Zondek or Friedman test will be positive. The eventual diagnosis is made at laparotomy, since for both types surgical treatment is indicated.

Sexual precocity in the female child has also been reported in association with cretinism,[55] with the injection of insulin[56] and with the presence of ovarian cyst.[57]

55. Kendle, F. W.: Case of Precocious Puberty in a Female Cretin, Brit. M. J. 1:246, 1905.

Pathologic Changes.—Granulosa cell tumors may be small or large, but usually they are of moderate size. They are soft, solid growths, usually well encapsulated. If rupture through their capsule or the attachment to surrounding organs has occurred (each does rarely occur in children) the tumor is likely to be malignant and should be treated as such. On section cystic spaces are often seen inside the tumor. The growths may be bilateral. Ascites may occur with them. Hypertrophy of the uterus is practically a constant observation in connection with granulosa cell tumor and is considered to be due to estrogens.

When examined histologically, the granulosa cell tumor is made up of immature and mature granulosa cells, some of which may be luteinized; in some cases many lutein cells are present. The cells are arranged in various patterns[58]; microfollicular, macrofollicular, cylindromatous or sarcomatous patterns may be seen.

Meyer[31] originally proposed that these tumors arose from nests of granulosa cells left over from the process of follicle formation. Most investigators are presently of the opinion that they arise from more primitive cells, the ovarian mesenchyma, from which also arise the theca cells.[59] This origin would explain the frequency with which mixtures of theca and granulosa cells occur in granulosa cell tumors. Novak and Brawner[60] reported that 28.1 per cent of their 33 cases of granulosa cell tumors were malignant; whereas, in the literature which they reviewed, incidence of malignancy among cases of these tumors was 5 to 10 per cent. According to Meigs[36] the incidence of malignancy varied from 5 to 25 per cent. Barzilai[58a] stated that tumors tend to recur after a long period, and there is no way histologically to predict which ones will recur or metastasize and which will not. Dockerty[15] stated, however, that the well encapuslated ones tend not to recur, and recurrence and metastasis are confined usually to those growths which occur among patients past the menopause.

Treatment.—Granulosa cell tumors of children should be treated conservatively with simple surgical removal, unless the tumor has invaded the surrounding structures, in which case panhysterectomy should be performed and postoperative roentgen therapy given.

REPORT OF A CASE

CASE 2.—A white girl, 17 months old, was admitted to the clinic because an abdominal tumor mass and slight vaginal bleeding had been present for two

56. Williams, G. A., and Williams, R. L.: Insulogenic Stimulation of Sexual Development, J.A.M.A. **104**:1208-1210 (April 6) 1935.

57. Mengert, W. F.: Precocious Puberty Due to an Ovarian Cyst in a Five Year Old Girl, Am. J. Obst. & Gynec. **37**:485-488 (March) 1939.

58. (*a*) Barzilai,[17] chap. 1, pp. 17-41. (*b*) Novak,[16] chap. 27, pp 344-356. (*c*) Meyer.[31] (*d*) Novak.[39]

59. Schiller.[18d] Meigs.[36] Novak.[39]

60. Novak, E., and Brawner, J. N.: Granulosa Cell Tumors of the Ovary. Am. J. Obst. & Gynec. **28**:637-649 (Nov.) 1934.

weeks. The family and past histories were not significant. On examination, development of the breasts, overdevelopment of the labia and the presence of pubic hair were noted, and a tumor was palpable in the lower part of the abdomen. The preoperative diagnosis was pelvic tumor.

At operation a large ovarian tumor was removed from and salpingo-oophorectomy performed on the right side. Marked ascites was present.

The tumor was large, firm, solid and lobulated. It was well encapsulated and was not attached to surrounding structures. It weighed 1,000 Gm. and measured 11 by 15 cm. The cut surface was yellow-brown, and small cystic spaces were present inside of the tumor. Sections from various parts of the tumor were studied

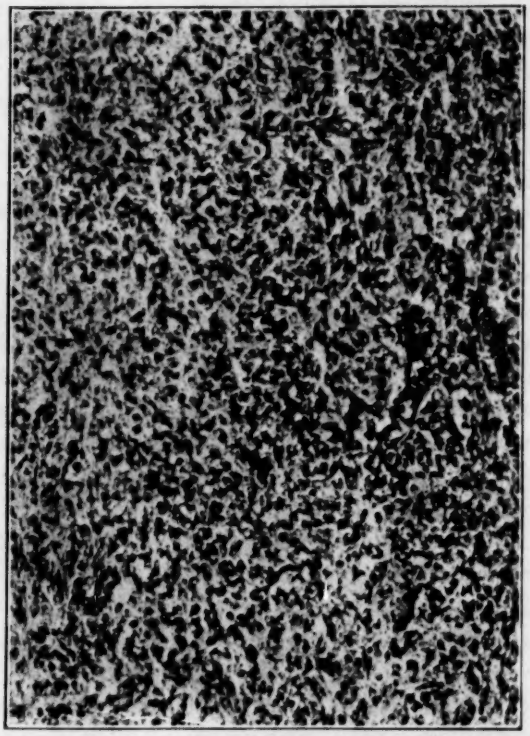

Fig. 4 (case 2).—Granulosa cell tumor showing diffuse pattern, hematoxylin and eosin; × 150.

microscopically (fig. 4). The granulosa cells appeared as moderate-sized, round or oval cells, with basophilic nuclei and prominent nucleoli. In some regions luteinized cells were seen. The cells were arranged in various patterns. The cylindroid pattern predominated, but follicular patterns occurred also. Some areas of hemorrhage and necrosis were present.

The patient made an uneventful recovery from the operation and was living and well seventeen years later.

SUMMARY AND COMMENT

Besides reviewing the literature on ovarian tumors in infants and children, we have reported data on 22 cases of ovarian tumor occurring in

infants and children 14 years of age and younger in which treatment was carried out at the Mayo Clinic during the past twenty-eight years.

More than 200 cases of ovarian tumor in infants and children have been reported in the literature. In approximately one third of these the tumors were simple multilocular cysts, in one fourth dermoid cysts, in more than one third carcinoma or sarcoma. In recent years the diagnosis of sarcoma and carcinoma of the ovary in children has become much less frequent, and it seems likely that many of the tumors which were reported as sarcoma or carcinoma in the older literature were granulosa cell tumors or dysgerminomas.

Simple cysts are relatively common ovarian tumors in infants and children. In our series of 22 cases, 7 were of simple cysts, an incidence of 31.8 per cent. Pain in the abdomen is the outstanding symptom, and torsion of the pedicle is a frequent complication. The latter event occurred in 5 of our 7 cases, an incidence of 71 per cent. Simple cysts with twisted pedicles are frequently confused clinically with appendicitis or appendical abscess.

Cystadenoma of the ovary is rare in children. The 3 in our series were all in children 14 years of age who had reached the age of puberty. Cystadenocarcinoma of the ovary in children is correspondingly rare.

Teratomas are the commonest ovarian tumor in children. In our series there were 10 cases, an incidence of 45.5 per cent. The dermoid cyst variety of teratoma was commoner than the embryonic type; there were 7 cases of dermoid cysts and 3 of embryonic teratomas in our series. The predominant symptoms are abdominal tumor and pain. Roentgenograms are useful adjuncts to the preoperative diagnosis of dermoid cyst. The dermoid cyst type of teratoma is usually benign, but the embryonic type must be considered as potentially malignant and frequently is.

One case of dysgerminoma occurred in our series, an incidence of 4.5 per cent. Dysgerminomas are unusual in that they frequently are associated with pseudohermaphroditism or genital hypoplasia. Opinions concerning the malignancy of dysgerminomas vary, but it is safest to consider them as definitely malignant tumors and to treat them as such with radical surgical procedures and postoperative roentgen therapy.

Granulosa cell tumors may occur in infants and children of any age but are uncommon. There was 1 case in our group, an incidence of 4.5 per cent. Granulosa cell tumor is a rare cause of sexual precocity in children and must be considered in the differential diagnosis of this condition. The incidence of malignant granulosa cell tumor in children is low.

Mayo Clinic.

USE OF A SUPPLEMENTED MILK FOR INFANT FEEDING

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KNOWLEDGE of the basic nutritional requirements of infants has progressed to the stage where the preparation of a completely supplemented milk is considered possible. The present study was undertaken to determine whether infants fed for nine months on such a supplemented milk with the addition of only carbohydrate and an unfortified cereal would exhibit normal growth and development and remain free from vitamin and mineral deficiencies. Although the exclusive use of such a preparation would not be desirable even if it were discovered to be nutritionally adequate, such a milk could serve a useful purpose in infant feeding. McCollum and Grubb[1] cited Dr. E. A. Park's opinion

that efforts to educate the public to the use of the necessary supplementary vitamins had progressed as far as possible and that if the infants who still suffered from deficiencies were to be protected a basic food with the necessary vitamins added must be made available.

Actual use of the milk product has brought to light other advantages, particularly the relief of anxiety of parents who can be assured that the milk contains the necessary supplemental substances in adequate amounts to insure proper growth. Moreover, the simplicity of its preparation and its availability in the form of sterile, stable canned evaporated milk greatly facilitates storage and transportation, features which enhance its value in periods of emergency and as a means of assistance to impoverished areas and illiterate peoples.

A milk preparation designed to meet these needs is now available.[2] A description of the development of the preparation and of its application

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From the New York Hospital and the Department of Pediatrics, Cornell University Medical College, and the New York Foundling Hospital.

This study was supported by a grant from the National Dairy Products Company, Inc., New York. The milk preparation used was "formulac."

1. McCollum, E. C., and Grubb, W.: A Completely Supplemented Evaporated Milk and Its Use as a Food for Infants, Am. J. Dis. Child. **68**:231 (Oct.) 1944.

2. The average composition of the test food ("formulac") is shown as given by McCollum and Grubb[1]: for each 100 Gm., water, 74.0 Gm.; total milk solids,

to infant feeding was published by McCollum and Grub in 1944.[1] They used accepted standards of growth to compare the weights and measurements of 83 infants fed this milk exclusively, and they concluded from this comparison and from the absence of clinical, roentgenologic and chemical evidence of vitamin deficiency that the food will support normal growth and development and will prevent vitamin deficiency.

In the present study, the nutritional status of a group of infants up to 21 months of age who were fed this supplemented milk exclusively during the first nine months of life was compared with that of a control group of infants fed currently recommended diets. The results of this controlled study confirm the observations of McCollum and Grubb that the preparation as the sole source of food will support normal nutritional growth and will prevent vitamin and mineral deficiency.

SUBJECTS

The study extended from April 1945 to April 1947 and involved infants who were under direct observation at the New York Foundling Hospital. This institution admits newborn infants who have been surrendered for adoption and infants and children under 2 years of age who have been abandoned or who are the victims of broken homes. Although admission to the institution is unrestricted as to color or racial origin, the infants are predominantly white.

All infants were less than 3 months old on admission to the study, and most of them remained in residence until they were at least 9 months old; all were in good physical condition and free from gross congenital defects. When they reached a weight-bearing age, a final study was made on the infants who had remained in the institution as well as on those who had been placed in foster homes.

GROUPING OF SUBJECTS

All infants in residence at the onset of the study and those admitted during its course[3] were distributed equally by color, sex and age among three groups,

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25.9 Gm.; protein, 7.0 Gm.; fat, 7.9 Gm.; carbohydrate, 9.0 Gm.; calcium, 0.2 Gm.; phosphorus, 0.2 Gm.; iron, 2.4 mg.; copper, 0.5 mg.; manganese, 0.5 mg.; vitamin A, 488 U.S.P. units; vitamin B_1, 0.24 mg. (81 U.S.P. units); vitamin C, 12.2 mg. (244 U.S.P. units); vitamin D, 122 U.S.P. units (now 195 U.S.P. units); riboflavin, 0.73 mg.; nicotinic acid, 1.22 mg.; biotin, 0.004 mg.; pantothenic acid, 0.73 mg.; copper, 0.49 mg., and manganese, 0.49 mg. (Caloric content is 139 calories per each 100 Gm.)

The test food ("formulac") was subjected to various procedures to check the stability of the vitamin C content as the least stable factor. Analyses of both undiluted milk and milk diluted with either cooled or boiling water showed no loss of total vitamin C content after storage at refrigerator temperature for twenty-four hours. These analyses for total vitamin C (free ascorbic acid and dehydroascorbic acid) by the phenylhydrazine method as modified by Lubschez[8] confirmed similar observations made by McCollum and Grubb[1] with the indophenol method.

3. For two periods, totaling thirteen weeks, admission to the study was discontinued because of an outbreak of diarrhea on the admission floor.

designated A, B and C, respectively. The infants in these groups were offered the following feeding regimens for the first nine months of life:

Group A[4] received test milk mixtures as the sole food until 6 months of age. At this time an unfortified cereal was added to the diet. No supplementary vitamins were given.

Group B[4] received evaporated milk mixtures with supplementary vitamins started at 2 weeks with the same unfortified cereal added at 6 months of age. Because the infants in this group appeared clinically to be progressing poorly, no infants were added to it after November 1945. The few infants entered in group B prior to this date, however, were continued on this feeding regimen.

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4. The detailed feeding regimens for the three groups were as follows:

Group A.—Milk: Test milk was prepared in exactly the manner usually employed for ordinary evaporated milk: dilution with the volume of water and fortification with the amount of a dextrin-maltose preparation ("dextri-maltose no. 2") calculated to give a dietary intake of calories, protein and fluid of 110 to 125 calories, 4.0 to 5.0 Gm., and 130 to 160 cc. per kilogram of body weight, respectively.

Vitamins: None were given.

Solid Foods: Only an unfortified cereal started at 6 months of age was given in quantities increasing to 2 ounces (60 Gm.) twice daily. The composition of this cereal ("farina," light) after cooking was as follows (Bradley, A. V.: Tables of Food Values, ed. 2, Peoria, Ill., The Manual Arts Press, 1942): protein, 1.6 per cent; fat, 0.2 per cent; carbohydrate, 11.4 per cent; calories, 54 per each 100 Gm.

Group B.—Milk: Usual mixtures of evaporated milk, water and a dextrin-maltose preparation were used in exactly the same dilutions and quantities as the test milk mixtures.

Vitamins: Vitamins A and D were started at 2 weeks of age and were given for the most part as cod liver oil in a dose increasing to 1 teaspoon (4 cc.) daily up to 9 months (9,000 units of vitamin A and 800 units of vitamin D per teaspoon). As a daily source of vitamin C, instituted at 2 weeks, 1 ounce (30 cc.) of orange juice or 25 mg. of ascorbic acid was given until 3 months of age, and 2 ounces (60 cc.) of orange juice or 50 mg. of ascorbic acid from 3 to 6 months. After the age of 6 months, 50 mg. of powdered ascorbic acid was given with the cereal.

Solid Foods: The same unfortified cereal was given from 6 to 9 months of age as for group A.

Group C.—Milk: The same mixtures of evaporated milk, dextrin-maltose and water as group B received were given.

Vitamins: Vitamins A and D were started at 2 weeks of age and continued as for group B. As a daily source of vitamin C, administration of 1 ounce of orange juice or 25 mg. of ascorbic acid was started at 2 weeks and continued until 3 months of age. Subsequently, 50 mg. of ascorbic acid powder was given with cereal.

Solid Foods: These foods in gradually increasing portions up to 2 ounces were given as follows: third month, cooked cereals—"ralston's," "maltex," oatmeal, "farina," corn meal; fourth month, vegetables—string beans, beets, carrots, spinach, squash, beet tops, peas, swiss chard, kale; sixth to ninth month, egg yolk; fruits—prunes, apricots, peaches, pears, apples; soups; "jello;" custards, meats—ground beef liver.

Group C[4] was offered a currently recommended diet. They received evaporated milk mixtures, with supplementary vitamins started at 2 weeks and solid foods started at 3 months of age.

PLAN OF STUDY

Each infant was given a complete physical examination on admission to the study and at monthly intervals thereafter until the ninth month. Lengths were measured with the infant in a trough, and a metal tape was used for determining the circumferences of the head and chest. The circumference of the head was measured over the greatest prominence of the occiput and glabella and that of the chest was taken in the nipple line at the end of expiration.

Complete blood counts were made, and fasting blood samples were drawn monthly for the first three months, then every two months. In addition to hemoglobin and hematocrit determinations, the blood samples were analyzed[5] for total protein, calcium, phosphorus, alkaline phosphatase, vitamin A and vitamin C. Vitamin C was determined on both plasma and the white cell-platelet layer (referred to in the table as vitamin C in white blood cells). Roentgenograms of the wrist were taken at 3, 6 and 9 months of age and at final check-up examination when possible. Urinalyses were performed monthly.

RESULTS

I. *Composition of Groups.*—A total of 114 infants were admitted to the study. Observations on 21 of the 114 infants were discontinued before three months from the time of admission to the study because of removal from the institution (13), illness (7) or death (1), and data on these infants were not included in the study. Of the 93 infants included in the analysis, 71 were under direct observation until at least 9 months of age; the remaining 22 were followed for at least three months. The distribution in the three groups by number and sex is shown in table 1. Because group B was abandoned early in the study, observations on these infants were too few to analyze separately. The identity of the dietary regimen of this group with that of group C

5. Hemoglobin was determined by photoelectric colorimeter, with a modification of the method of Evelyn (Evelyn, K. A.: J. Biol. Chem. **115**:63, 1936) and serum protein by the refractometric method of Neuhausen and Rioch (Neuhausen, B. S., and Rioch, D. M.: ibid. **55**:333, 1923). The Clark-Collip modification of Tisdall's method was used for determination of calcium (Clark, E. P., and Collip, J. B.: ibid. **63**:461, 1925), that of Fiske and Subbarow for phosphorus (Fiske, C. H., and Subbarow, Y.: ibid. **66**:375, 1925) and the micromethod of Bessey, Lowry and Brock for alkaline phosphatase (Bessey, O. A.; Lowry, O. H., and Brock, M. G.: ibid. **164**:321, 1946). Analyses of plasma for vitamin A were made by the micromethod of May and associates (May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 [June] 1940). Plasma vitamin C was determined by the phenylhydrazine method of Roe and Kuether (Roe, J. H., and Kuether, C. A.: J. Biol. Chem. **147**:399, 1943) and amount of vitamin C in white blood cells according to the method of Lubschez.[8]

during the first three months permitted its inclusion with the control group during this time. Thereafter, the control group was composed of group C alone. The resulting distribution of the control group (44 infants) and of the test group (group A with 49 infants) by sex is also shown in table 1. Although observations were made monthly or bimonthly for nine months and then every three months as shown in table 1, only the results of the observations for the first, third, sixth and ninth months and the sixteenth and eighteenth months are presented in the tables that follow. The number of infants in the test and control groups observed at the ages selected is shown in bold face type in table 1.

TABLE 1.—*Distribution of Infants Observed at Various Ages by Groups and Sex*

Age, Mo.	Number of Infants Observed											
	Test Group									Control Group 1 to 8 Mo. of Age: B and C Over 4 Mo. of Age: C Only		
	A			B			C					
	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls
1	**29***	16	13	6	3	3	12	7	5	18	10	8
2	43	25	18	12	6	6	22	11	11	34	17	17
3	**49†**	28	21	15	8	7	26	14	12	**41***	22	19
4	45	25	20	16	9	7	27	14	13	27	14	13
5	45	26	19	14	8	6	28	15	13	28	15	13
6	41	23	18	14	8	6	27	14	13	27	14	13
7	35	19	16	14	8	6	23	15	8	23	15	8
8	31	16	15	13	7	6	21	12	9	21	12	9
9	29	17	12	14	8	6	22	11	11	22	11	11
10	7	3	4	3	1	2	3	2	1	3	2	1
13-15	9	5	4	1	1	0	6	3	3	6	3	3
16-18	12	7	5	7	4	3	6	5	1	6	5	1
19-21	6	2	4	6	3	3	7	4	3	7	4	3
22 and over	1	1	0	1	1	0	1	0	1	1	0	1

*Numbers in bold face type in this and the following tables represent the infants in the test and control groups observed at the ages selected.

†Largest number of infants in test and control group observed at any one age.

II. *Clinical Appraisal of Nutritional Status.*—In the interpretation of clinical status, it should be borne in mind that these infants were, in a literal sense, handicapped infants. The institutional environment, the absence of individual attention and the circumstances of their admissions, all exerted a distinctly adverse effect on their growth and development. Empathy, which is of relatively small concern in private practice, is of great moment in institutional work. Failure to gain without demonstrable cause for periods ranging from one to two weeks after admission occurs frequently. Comparisons, therefore, are valid only between groups within the study and not between this and other series of infants.

Although no systematic clinical evaluation was attempted, it was the impression of the observers that the general progress of the infants in the test group was equal in every recognizable respect to that of the infants in the control group. The two groups of infants were alike in their general appearance, their attitude and their behavior as judged by Gesell and Amatruda's inventory[6] and by the developmental steps of neuromuscular growth, including the time of appearance of smiling, vocalizing, head control, hand control, rolling, sitting, crawling, prehension, pulling-up, walking with support, standing alone and walking alone, as suggested by Aldrich and Norval.[7]

The test milk proved as acceptable in taste as plain evaporated milk mixtures except to a few infants in the second month of life who had been receiving an excessively sweetened formula before admission. The incidence of loose stools immediately following admission did not vary appreciably between groups, and at no time was the test milk discontinued because of vomiting, diarrhea or unacceptability attributed to the milk itself.

Interpretation: No difference between the two groups in general clinical progress, in acceptance of the feeding or in the incidence of gastrointestinal upsets and infections was observed. Insofar as clinical impressions may be relied on to appraise growth and development, it may be inferred that the infants fed the supplemented milk thrived as well as those fed currently recommended diets.

III. *Appraisal of Nutritional Status from Anthropometric Measurements.*—Mean values and standard deviations for weight, height and circumference of head and chest for the two groups of infants at the stated ages are shown in table 2. In this and the following tables the values shown for the selected months were not significantly different from those for the intervening months and, therefore, are considered to be truly representative. It is evident that there was no significant difference in the values obtained for weight, height and circumference of head or chest between the two groups.

A. Height and Weight: A total of 702 height measurements and 708 weighings of the 93 subjects was analyzed. The small differences in the means and larger standard deviations indicated no difference in growth in height or weight between the test and control groups.

B. Circumferences of Head and Chest: Six hundred and eighty-four and 683 measurements of circumferences of head and chest, respectively,

6. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis and Supervision, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 1, chap. 9, p. 1.

7. Aldrich, C. A., and Norval, M. A.: A Developmental Graph for the First Year of Life, J. Pediat. **29**:304, 1946.

were analyzed. No difference between the two groups in growth in circumference of head and chest is apparent from the almost identical values of the means.

The time of eruption of teeth in the two groups is shown in table 3, in which the number and percentage of infants having the stated num-

TABLE 2.—*Anthropometric Measurements of Infants in Test and Control Groups at Selected Ages*

Age, Mo.	Group	Weight, Kg.			Height, Cm.			Circumference of Head, Cm.			Circumference of Chest, Cm.		
		No. of Infants	Mean	S.D.*	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.
1	Test	28	3.28	0.47	27	50.5	1.3	28	34.9	1.8	28	32.9	2.1
	Control	18	3.21	0.50	18	51.3	2.8	17	35.6	2.2	15	32.6	1.5
3	Test	49	4.51	0.59	49	57.2	3.0	47	37.9	1.6	46	36.3	1.6
	Control	39	4.33	0.54	39	57.3	2.8	36	37.9	1.7	35	36.1	2.0
6	Test	40	6.51	0.84	41	64.8	2.6	41	41.0	1.8	40	40.6	1.4
	Control	25	6.42	0.65	26	64.2	2.4	25	41.0	1.4	23	40.4	0.9
9	Test	26	8.17	1.04	27	69.6	1.6	26	43.1	1.6	25	43.9	2.2
	Control	21	8.09	0.63	21	68.8	1.6	20	43.4	1.2	21	43.7	1.7
16 to 18	Test	10	10.58	1.13	10	78.9	3.2	10	46.8	1.4	10	47.6	1.8
	Control	4	11.68	1.29	4	82.5	2.7	4	48.0	0.8	4	49.2	2.1

*Standard deviation.

TABLE 3.—*Age at Onset of Dentition in Infants of Test and Control Groups*

No. of Teeth	Test Group Age, Mo.								Control Group Age, Mo.							
	3		6		9		16 to 18		3		6		9		16 to 18	
	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent
0	49	100	36	87.8	14	51.9	—	—	39	100	25	96.2	6	28.6	—	—
1	—	—	2	4.9	4	14.8	—	—	—	—	1	3.8	2	9.5	—	—
2	—	—	3	7.3	7	25.9	—	—	—	—	—	—	6	28.6	—	—
3 to 4	—	—	—	—	0	—	—	—	—	—	—	—	6	28.5	—	—
5 to 6	—	—	—	—	2	7.4	1	10	—	—	—	—	1	4.8	—	—
7 to 10	—	—	—	—	—	—	5	50	—	—	—	—	—	—	—	—
11 to 16	—	—	—	—	—	—	4	40	—	—	—	—	—	—	4	100
Totals	49	100	41	100	27	100	10	100	39	100	26	100	21	100	4	100

ber of teeth at the given ages are shown. The table shows that at 6 months of age the percentage of infants having teeth is slightly higher in the test group than in the control group. At 9 months of age a greater difference exists, with a higher percentage of the control group having teeth. Neither of these differences, however, is statistically significant.

Interpretation: No significant differences in growth in weight, height and circumference of head and chest or in time of onset of dentition between the test and control groups were observed. Insofar as these measurements appraise nutritional status, it may be inferred that the infants receiving supplemented milk ("formulac") thrived as well as infants fed currently recommended diets.

V. *Appraisal of Nutritional Status from Chemical Examinations of Blood.*—Mean values and standard deviations for blood serum levels of protein, calcium, inorganic phosphorus, alkaline phosphatase, carotene, vitamin A, and for vitamin C in plasma and white blood cells for the infants of the two groups at the ages stated are shown in table 4. Examination of the table reveals that although there is more irregularity in the mean values than appeared in the physical measurements, no consistent difference between the two groups is present.

A. Serum Protein: A total of 517 determinations of serum protein levels of the 93 infants revealed no real difference between the two groups. The expected low standard deviations and the gradual increase in the mean values with growth are apparent from the table.

B. Serum Calcium and Inorganic Phosphate: A total of 507 determinations of serum calcium in 93 infants showed its constancy throughout the period of study with no difference between the two groups. The values for inorganic phosphate in 502 determinations exhibited the expected decrease in concentration during the first year, but no significant difference between the two groups was seen.

C. Serum Alkaline Phosphatase: A total of 514 determinations of serum phosphatase was analyzed. Values for those infants (13) showing suggestive and definite (2) roentgenologic signs of rickets were analyzed separately. Values for the normal infants are shown in table 4, and it may be seen that there is no significant difference between the mean values for the test and the control groups, and no infant in either group had a phosphatase level of more than 20 millimols per hour. Two infants in the control group with roentgenologic evidence of rickets had phosphatase levels of 30.2 and 67.4 millimols per hour, respectively. If the infants with these two phosphatase levels are eliminated, the mean and range of values for serum phosphatase in the remaining infants showing suggestive roentgenologic evidence of rickets was 9.4 with a range of 7.4 to 16.3 millimols per hour; whereas the mean value for 64 infants showing no such evidence was 8.7 with a range of 3.0 to 17.2 millimols per hour. The expected decrease in levels of serum phosphatase with increasing age is apparent.

D. Plasma Carotene and Vitamin A: Five hundred and twelve and 508 determinations of carotene and vitamin A, respectively, were analyzed. The values for both measurements show no significant differ-

TABLE 4.—*Results of Chemical Examinations of Blood of Infants in Test and Control Groups at Selected Ages*

Age, Mo.	Group	Protein, Gm./100 Cc.			Calcium, Mg./100 Cc.			Phosphorus, Mg./100 Cc.			Alkaline Phosphatase, mM./Hr.			Carotene, May Units/100 Cc.			Vitamin A in May Units/100 Cc.			Vitamin C in Plasma, Mg./100 Cc.			Vitamin C in White Blood Cells, Mg./100 Gm.		
		No. of Infants	Mean	S.D.*	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.
1	Test	21	5.8	1.0	21	9.8	0.2	20	6.6	0.7	19	5.5	1.8	20	5.6	3.5	20	8.4	2.6	19	0.4	0.2	19	16.7	6.6
	Control	10	6.0	0.2	8	10.0	0.9	7	6.5	0.8	9	7.5	1.9	10	4.3	2.9	10	6.9	2.5	10	0.2	0.2	9	14.1	6.0
3	Test	42	5.9	0.5	42	9.8	0.6	42	6.3	0.6	36	8.2	2.6	43	6.6	5.0	42	9.8	3.6	43	0.7	0.3	44	22.6	5.6
	Control	35	5.7	0.6	35	9.6	0.3	35	6.1	0.7	28	9.4	3.0	36	6.0	4.4	36	9.1	3.1	37	0.4	0.4	37	17.6	7.8
6	Test	21	6.4	0.4	21	9.8	0.4	21	6.0	0.9	19	8.5	4.1	21	8.2	4.8	21	10.2	4.0	19	0.9	0.4	21	24.3	4.9
	Control	16	6.5	0.5	16	10.0	0.5	16	5.7	0.9	11	8.6	3.5	16	12.2	9.1	16	11.6	3.9	16	0.8	0.4	16	23.6	5.9
9	Test	19	6.6	0.4	18	9.7	0.5	19	6.0	0.2	15	6.1	1.3	19	10.6	7.3	19	10.2	3.8	19	1.1	0.3	19	22.5	4.2
	Control	11	6.5	0.9	11	9.6	0.3	11	5.6	0.9	9	6.2	1.9	11	36.8	19.8	11	15.2	6.7	10	1.1	0.5	11	24.3	4.6
16 to 18	Test	10	6.9	0.5	10	10.0	0.3	10	5.3	0.5	8	5.7	1.3	9	117.3	90.5	8	19.9	12.1	10	0.8	0.4	10	20.8	6.1
	Control	6	6.9	0.7	6	9.8	0.6	6	5.8	0.6	5	6.1	0.9	6	88.9	42.9	6	14.7	6.2	6	1.0	0.4	6	25.5	4.2

*Standard deviation.

ence between the two groups at 1 and 3 months of age. A steady increase in levels of plasma carotene and vitamin A with increasing age is apparent in both groups. The irregularity of the values in the later months is expected and shows no constant trend. This irregularity and wide spread is noticed particularly in the values for carotene.

E. Vitamin C in Plasma and White Blood Cells: Results of 503 determinations of vitamin C in plasma and of 529 in white blood cells reveal no significant difference between the two groups. The values shown for vitamin C in white blood cells in both groups of infants are within the range of values reported by Lubschez for children.[8] No values for infants for this determination have been reported previously.

Interpretation: Insofar as general nutritional status can be appraised from serum protein levels and adequacy of intake of: (1) vitamin D from serum calcium, phosphorus and alkaline phosphatase levels; (2) vitamin A from serum carotene and vitamin A levels, and (3) vitamin C from plasma and levels of vitamin C in white blood cells, it may be inferred from the results that the infants fed only the supplemented milk ("formulac") thrived as well as those fed a currently recommended diet.

VI. ***Hematologic Examination.***—Mean values and standard deviations for hemoglobin levels, per cent hematocrit, red and white blood cell counts and differential counts for the two groups at the selected ages are shown in table 5. Analysis shows no consistent difference between the two groups.

A. Hemoglobin, Hematocrit and Red Blood Cell Counts: The mean values for 501, 488 and 529 determinations, respectively, of the hemoglobin levels, per cent hematocrit and red blood cell counts are practically identical for the two groups. The expected initial fall in these values during the first three months and the subsequent rise are apparent.

B. White Blood Cell and Differential Counts: No significant difference in the mean for 529 white blood cell and differential counts is noted between the two groups.

Interpretation: Red blood cell and hemoglobin levels were used to appraise general nutritional status and adequacy of iron intake. Although no foods containing iron other than the test milk were given to the infants in the test group during the first nine months, their levels of hemoglobin and values for red blood cell counts and hematocrit were equal to those of the control group.

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8. Lubschez, R.: Studies in Ascorbic Acid with Especial Reference to the White Layer: I. Description of Method and Comparison of Ascorbic Acid Levels in Whole Blood, Plasma, Red Cells and White Layers, J. Clin. Investigation **24**:573, 1945.

TABLE 5.—*Results of Hematologic Examinations on Infants in Test and Control Groups at Selected Ages*

Age, Mo.	Group	Hemoglobin, Gm./100 Cc.			Hematocrit, %			Red Blood Cells, Millions/Cu. Mm.			White Blood Cells, Thousands/Cu. Mm.		Polymorphonuclear Leukocytes				Lymphocytes, %	
													Mature, %		Band, %			
		No. of Infants	Mean	S.D.*	No. of Infants	Mean	S.D.	No. of Infants	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1	Test	17	14.2	1.9	16	42.3	7.5	20	4.49	0.22	11.8	4.3	32	7	7	3	61	10
	Control	8	14.1	2.2	8	45.4	3.4	13	4.56	0.34	11.8	4.0	26	8	7	6	66	10
3	Test	42	10.4	1.1	39	32.3	3.1	45	3.99	0.28	11.6	3.9	28	9	5	3	66	11
	Control	37	10.4	0.8	34	33.3	2.7	37	4.00	0.34	10.5	2.9	25	7	4	2	71	9
6	Test	21	11.1	1.1	21	34.8	2.5	23	4.24	0.23	11.9	2.9	29	10	4	3	67	11
	Control	16	11.1	1.4	16	36.5	2.7	17	4.23	0.24	11.3	3.6	29	6	5	2	66	8
9	Test	19	11.4	1.2	19	37.7	1.9	19	4.34	0.22	12.6	2.4	28	5	4	2	68	6
	Control	11	10.5	1.4	11	35.3	3.6	13	4.24	0.36	12.3	2.5	28	5	5	3	67	8
16 to 18	Test	9	11.3	1.0	10	37.7	2.4	9	4.48	0.23	11.4	2.9	35	8	5	2	60	9
	Control	6	11.8	0.8	6	38.3	1.7	6	4.34	0.41	12.8	2.6	32	6	7	2	61	8

*Standard deviation.

VII. *Appraisal of Nutritional Status and Adequacy of Intake of Vitamins D and C from Roentgenologic Examinations.*[9]—A total of 313 roentgenograms of the wrists were taken of the 93 infants whose clinical and laboratory data comprise the basis of this report. Seventy-one patients were examined roentgenographically at 3, 6 and 9 months of age; 7 at 3 and 6 months, and 14 at only 3 months. One patient, who was in the study for three months, was not examined in this manner. Of the 71 patients on whom three roentgenograms were made, 56 were again studied by roentgenograms at a weight-bearing age.

Method: To avoid bias, the initial readings were made without resort to clinical and laboratory data. Particular attention was paid to: (1) lipping, (2) rarefaction and irregularity of the epiphysial plate and (3) condensation. The individual films were given a grade ranging from 0 to 5 plus on each of these criteria. This grading served as an initial screening, and when a film received a total of 5 plus with at least 1 plus for rarefaction and irregularity at the epiphysial plate, the roentgenogram was studied in conjunction with the clinical and laboratory data.[9] Films receiving a total of 5 plus or over in lipping and condensation alone were not considered significant. At the termination of the study, all the films were again examined in conference with the roentgenologist and questionable films were discussed in the light of clinical data.

None of the roentgenograms showed evidence of frank avitaminosis. Seven infants in the test group and 5 infants in the control group demonstrated minimal changes in one roentgenographic examination, although at the time the roentgenograms were reported on their clinical and chemical findings were satisfactory. One infant in the control group showed minimal changes on two successive examinations. These changes were interesting because the child, a girl, had been born prematurely (weight at birth, 2,041 Gm.) and, in addition, had received a course of roentgen therapy for an enlarged thymus at another institution. The roentgenograms taken at 3 months, one month after this therapy, showed minimal changes. At that time, the value for phosphatase was 30.2 millimols per hour. When she was 6 months of age, the film still showed minimal changes, although the phosphatase values determined in the intervening time had fallen to normal. For this infant, as for all the other infants who showed minimal changes, the roentgenograms and clinical and chemical values returned spontaneously to within normal limits.

The centers of ossification at the wrist were recorded in all films. The time of appearance of the centers in the two groups is shown in

9. Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology, Chicago, The Year Book Publishers, Inc., 1945.

table 6, in which the number and percentage of infants with the stated number of centers at the stated age are shown. It can be seen that there is no significant difference between the two groups in the time of appearance of ossification centers.

Interpretation: Roentgenograms of the wrist were employed to appraise general nutritional status and adequacy of intake of vitamins D and C. Insofar as the roentgenologic appearance of the bone reflects these factors, it can be inferred that the status of infants fed the supplemented milk ("formulac") was equal to that of infants offered a presumably ideal diet.

COMMENT

The data indicate that, as the sole source of food for the first nine months of life, a supplemented evaporated milk with the addition of only carbohydrate and an unfortified cereal will support normal growth

TABLE 6.—*Time of Appearance of Centers of Ossification in Infants of Test and Control Groups*

No. of Centers	Test Group Age, Mo.						Control Group Age, Mo.					
	3		6		9		3		6		9	
	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent	No. of Infants	Per Cent
0	22	45.8	2	4.7	—	——	14	31.8	3	10.3	2	8.7
1	9	18.8	9	20.9	1	3.0	12	27.3	3	10.3	—	——
2	16	33.3	27	62.8	22	66.7	17	38.6	22	75.9	15	65.2
3	1	2.1	4	9.3	8	24.2	1	2.3	1	3.4	6	26.1
4	—	——	1	2.3	2	6.1	—	——	—	——	—	——
5	—	——	—	——	—	——	—	——	—	——	—	——
Totals	48	100.0	43	100.0	33	100.0	44	100.0	29	100.0	23	100.0

and development and will prevent recognizable vitamin and mineral deficiencies. Without the addition of vitamins or foods containing minerals infants fed the supplemented milk showed no clinical, biochemical or roentgenologic evidence of rickets or scurvy and no clinical or hematologic evidence of iron deficiency. Laboratory evidence of these vitamin deficiencies in infants receiving inadequate intakes during the first nine months is expected with sufficient regularity to justify the conclusion that the vitamin C and D levels of the supplemented milk were effective in preventing these deficiencies.[10]

10. It would have been gratifying had we been able to demonstrate that the iron content of the supplemented milk prevented iron deficiency. However, it must be pointed out that the 16 infants in the original group B who received vitamin but no mineral supplements had hemoglobin and hematocrit values and

On the other hand, although extended anthropometric, biochemical, hematologic and roentgenologic measurements were made in an attempt to assess the general nutritional status and physical growth of the infants, clinical appraisal proved more serviceable for definitive evaluation. As an example, although one of the original groups (group B) appeared clinically to be progressing so poorly that it was considered improper to continue the group, anthropometric and laboratory evidence of this poor progress was not demonstrable. This reaffirms the relative crudity of present methods in evaluating general nutritional status by cross sectional measurements in the absence of specific deficiencies.

If the measurements made in this study do not adequately reflect general nutritional status, what additional observations may contribute to such an evaluation? The remarkable constancy, particularly of the biochemical and hematologic measurements, as shown by the small differences between the mean values for the two groups and by the low standard deviations for each group, suggests that the time and effort consumed in making more of the same observations would not contribute worth while additional information. A similar limitation would apply to the continuation of the same observations for a longer period of time. Although not within the scope of the present study because of the large number of subjects and the extensive clinical observations required over a prolonged period, it is suggested that systematic clinical appraisal might provide a more definitive evaluation of general progress. In such a study, attention could be focused on such developmental tests of neuromuscular growth as Aldrich and Norval suggested[7] or preferably on the more quantitative developmental diagnostic procedures of Gesell and Amatruda.[6] Inclusion of studies on immunologic responses and clinical susceptibility to infections in these large groups of infants might yield additional information of value.

SUMMARY AND CONCLUSIONS

Observations are reported on a total of 93 infants who were for the most part in residence at an institution during the first nine months of life. Of these infants, 49 were offered a supplemented evaporated milk mixture ("formulac") with the addition of only carbohydrate and an unfortified cereal as the sole source of food until 9 months of age. The remaining 44 were offered a currently recommended complete diet. In addition to clinical observations on the infants, anthropometric, biochemical, hematologic and roentgenologic measurements were made monthly

red blood cell counts that were no lower than those for the other two groups. This failure to find laboratory evidence of iron deficiency in the infants of group B4 can be attributed only to the greater individual variability of response to iron deficiency than to vitamin deficiency and to the paucity of infants so studied.

or bimonthly for the first nine months of life and as follow-up studies thereafter. The clinical progress of the two groups is noted and the quantitative data analyzed and compared.

General clinical progress of the two groups of subjects was equally satisfactory. No clinical or laboratory evidence of nutritional deficiency was discovered, and analysis of the anthropometric, biochemical, hematologic and roentgenologic measurements revealed no significant differences between the two groups.

Insofar as these observations measure nutritional status, it may be concluded that, as the sole source of food for the first nine months of life, a supplemented evaporated milk with the addition of only carbohydrate and an unfortified cereal will support normal physical growth and development and will prevent vitamin and mineral deficiencies.

525 East Sixty-Eighth Street (21).

The following persons aided in this study:

Dr. Juan Julia and Dr. Alvah Weiss assisted in the management and observation of the infants, as well as in the collection of the specimens. Dr. B. Aubrey Schneider and Miss G. Freedman assisted in the statistical analyses and interpretation. Dr. Charles Oderr, roentgenologist at the New York Foundling Hospital, interpreted the roentgenograms. Miss R. Lubschez made the determinations of vitamin C. The Sisters of Charity and the nurses of the New York Foundling Hospital were responsible for the general care of the infants.

INHALATION THERAPY IN PEDIATRICS

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AND
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IN RECENT years inhalation therapy has achieved ever increasing importance in maintaining respiratory function, owing mainly to the pioneering efforts of Barach, Segal and their co-workers in this field. With the introduction of administration of antibiotic substances by inhalation as an aerosol the scope of this type of therapy was broadened considerably.

The efficacy of penicillin aerosol therapy and its physiologic rationale have been well established.[1] For many conditions occurring with greatest frequency in the pediatric age group aerosol penicillin is definitely indicated. However, the application of inhalation therapy in pediatric practice has several limitations. These are due chiefly to the fact that the most satisfactory methods at present are designed for adults and are not easily adaptable to use for persons in the younger age groups, since cooperation of the patient is not possible. It therefore becomes necessary to devise new methods which are adaptable to pediatric practice.

Several technics for use with infants and children have been described.[2] In some cases the equipment used has proved cumbersome, in-

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1. Mutch, N., and Rewell, R. E.: Penicillin by Inhalation, Lancet **1**:650-652 (May 26) 1945. Bryson, V.; Sansome, E., and Laskin, S.: Aerosolization of Penicillin Solutions, Science **100**:33-35 (July 14) 1944. Segal, M. S., and Ryder, C. M.: Penicillin Aerosolization in the Treatment of Serious Respiratory Infections, New England J. Med. **233**:747-756 (Dec. 20) 1945. Knott, F. A., and Clark, W. H.: Absorption of Aerosol Penicillin Via the Lungs, Lancet **1**:468-469 (April 14) 1945. Barach, A. L.; Silberstein, F. H.; Oppenheimer, E. T.; Hunter T., and Soroka, M.: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess: Preliminary Report, Ann. Int. Med. **22**:485 (April) 1945.

2. (*a*) Prigal, S. J.; McGavack, T. H.; Speer, F. D., and Harris, R.: Aerosol Penicillin, J.A.M.A. **134**:932-938 (July 12) 1947. (*b*) Segal, M. S., and Ryder, C. M.: Penicillin Inhalation Therapy, New England J. Med. **236**:132-138 (Jan. 23) 1947. (*c*) Vermilye, H. N.: Aerosol Penicillin in General Practice, J.A.M.A. **129**:250-257 (Sept. 22) 1945.

efficient and discomforting to the patient, as well as time consuming and expensive in practical operation. Furthermore, not all these methods are applicable to infants under 1 year of age. The hood apparatus is most generally used at present, but it has many of the disadvantages aforementioned.

We have devised several new technics in our pediatric service which we believe desirable to report at this time, as they may be found useful by others. Since the effectiveness of inhalation therapy depends to a large extent on the type of equipment used, we attempted to design an

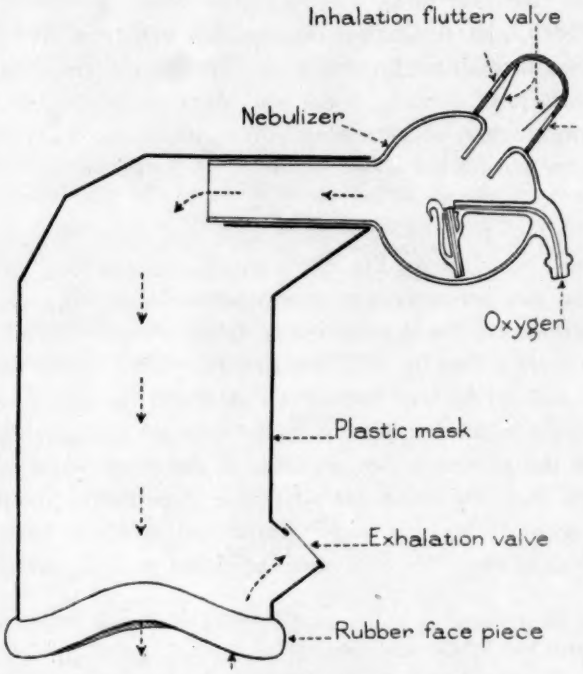

Fig. 1.—Diagram illustrating principle of the aerosol penicillin mask.

apparatus simple in construction yet with maximum efficiency, one which may be simply and easily operated, which is relatively inexpensive and applicable to patients of all age groups and which might also be used in the office or home, where gases under pressure are not readily available. It was our objective that this apparatus be used not only in the treatment of diseases of the respiratory tract but also as a means of administering penicillin in the treatment of systemic disease for which adequate blood levels are required.

The apparatus (fig. 1) consists of a "vaponefrin" nebulizer,[3] to which an inhalation value over the upper carburetor opening has been added, and a plastic mask made in the shape of a curved cone with a soft rubber face piece and ex-

3. The nebulizer was manufactured by the Vaponefrin Co., Upper Darby, Pa.

halation valve. The spout of the nebulizer fits securely into the top of the mask. This connection is air tight yet remains freely movable, so that the nebulizer can be rotated or separated from the mask.

The mask may be made by any thin, flexible plastic material. Our first models were made of washed x-ray films, which proved satisfactory. Soft rubber tubing was used for the face piece, which was sealed to the lower edge of the mask.

The inhalation valve may be made from the cap of a plastic "benzedrine" inhaler. Two or three holes are cut in the sides of the cap, and the finger tip of a rubber glove is secured to the top of the inside of the cap, thus forming a simple flutter valve. The exhalation valve may be made by cutting a small hole in the lower portion of the mask and placing over this opening a piece of rubber tissue, which is then sealed to the mask along one or two edges.

This apparatus is a closed system from which, by virtue of the valves, the necessity for a rebreathing bag has been eliminated; there is no possibility of accumulation of carbon dioxide, and the patient is not dependent on the oxygen or on the air-producing nebulization for his metabolic needs.

The inhalation valve prevents loss of penicillin during exhalation and eliminates the necessity for the demand type of oxygen regulator such as that used by Eckman and associates[4] and other investigators. During inhalation it is possible to inspire only air which passes through the nebulizer and the mist which has accumulated in the upper portion of the mask during exhalation.

For the administration of a single dose, the desired amount of penicillin in solution is placed in the nebulizer; the mask is then placed over the patient's face, and the flow of oxygen is started. The rate of nebulization depends on the flow of oxygen and may be maintained at any desired level. We have found it preferable to keep the flow of oxygen from 3 to 6 liters per minute, depending on the size of the patient. If the rate of flow of oxygen or air is greater than the respiratory exchange, considerable amounts of penicillin will be lost during exhalation.

The time required for a single administration is much less than that required with the intermittent technic as nebulization with this apparatus is continuous throughout the respiratory cycle. Since a continuous flow of oxygen or air is not necessary, pressures produced by hand to actuate nebulization are brought into the realm of practicability. Either the hand bulb or a tire pump can be used satisfactorily. The latter, however, is preferable to the bulb. For use in hospitals, oxygen is the most readily available and most convenient source of gas.

We have found this method applicable to persons of all age groups, with equal effectiveness. Our youngest patient receiving this therapy was 10 days of age. Some resistance is encountered in children under 3 years of age, but this usually ceases to be a problem after the child has received the second or third dose.

Review of the literature reveals that the doses used by various authors ranged from 1,000[5] to 2,000,000 units[6] daily. The frequency of administration varied from

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4. Eckman, M.; Rumsey, C. C., Jr.; Barach, B., and Barach, A. L.: Demand Apparatus for Automatic Delivery of Aerosols During Inspiration, J. Lab. & Clin. Med. **30**:608-610 (July) 1945.

5. Hanks, R. J.: Nebulized Penicillin in Treatment of Respiratory Infections, Texas State J. Med. **41**:253-254 (Sept.) 1945. Vermilye.[2e]

6. (*a*) Barach, A. L.; Garthwaite, B., and Soroka, M.: For the Inhalation of Penicillin Aerosol, Mod. Hosp. **66**:100 (Feb.) 1946. (*b*) Segal, M. S.: Inhalation Therapy in Treatment of Serious Respiratory Disease, New England J. Med. **229**:235-241 (Aug. 5) 1943. (*c*) Hagens, E. W.; Karp, M., and Farmer, C. J.: Inhalation Method for Penicillin Therapy: Preliminary Report, Arch. Otolaryng. **41**:333-336 (May) 1945.

once[3c] to sixteen[6c] times a day. As yet we have not established a definite scale of doses, but our present data indicate that a dose one-fourth greater than the intramuscular dose is necessary at intervals of three hours.

Only isotonic solution of sodium chloride is used as a solvent. A single dose is dissolved in 0.5 or 1 cc., depending on the size and weight of the patient: One-half cubic centimeter is used for infants under 1 year of age and 1 cc. for all older children. It was found that to nebulize the last few drops of each dose the duration of administration was prolonged by two to three minutes.

Repeated determinations were made of the volume remaining in the nebulizer after the solution was cleared from the bottom of the chamber. This volume amounted to approximately 0.2 cc. To make up for this loss, an additional 0.2 cc. of the solution is added to the original dose and treatment stopped when fluid is no longer visible in the bottom of the chamber. After administration is completed, a cork stopper is placed in the spout of the nebulizer. The amount remaining will make up the deficit of the next dose. Recently, we have used only crystalline penicillin G. It has not been found as objectionable in odor and taste as is the amorphous penicillin.

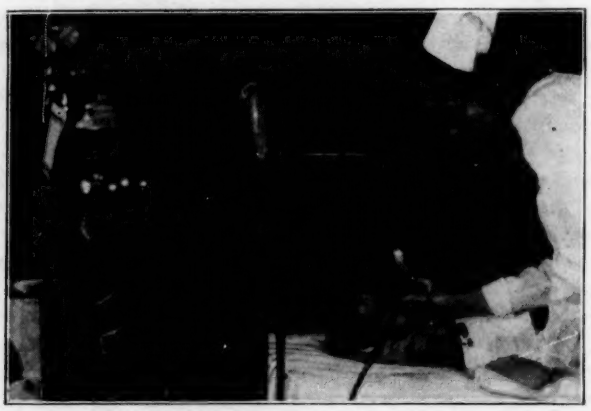

Fig. 2.—Photograph showing administration of aerosol penicillin to a child 2½ years of age with fibrocystic disease of the pancreas.

Determinations of the blood level of the drug for children with normal respiratory and excretory function indicate that penicillin when inhaled by this method enters the blood stream rapidly and reaches a peak early.

A typical curve is shown in figure 3. A detailed report of blood level studies and clinical results will be included in a subsequent paper.

HUMIDIFICATION

It is well established that an atmosphere of high relative humidity is of extreme importance in the treatment of certain diseases of the respiratory tract. This belief is based not only on clinical observation but on experimental evidence.[7]

7. Holinger, P.; Bash, F. P., and Poncher, H. G.: Influence of Expectorants and Gases on Sputum and Mucous Membranes of Tracheobronchial Tree, J.A.M.A. **117**:675-678 (Aug. 30) 1941.

The most commonly used means of humidification at present is steam. However, in order to attain the desired humidity by use of steam, either in a room or in a croup tent, the resultant increase in temperature not only becomes oppressive and unbearable but increases the metabolic rate and, in turn, the respiratory effort. The loss of fluids through perspiration at these temperatures further contributes to the dehydration of the patient.

It is essential, then, that if the patient is to derive the greatest benefit from high relative humidity the atmosphere be kept at a comfortable temperature, preferably between 70 and 76 F.[8] In many cases of infections of the respiratory tract, in which a high degree of humidity is indicated, dyspnea is also present. It therefore becomes apparent that to produce ideal conditions oxygen also should be introduced into the atmosphere. In an effort to fulfil these requirements without elaborate and expensive equipment, we devised the apparatus shown in figure 4.

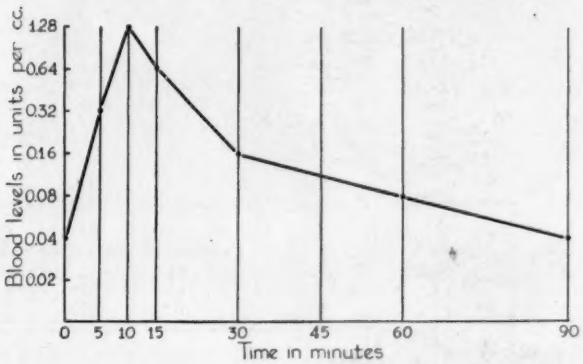

Fig. 3.—Curve for mean blood level for 5 normal children 6 weeks to 12 years of age, showing maximum concentration occurring ten minutes after inhalation. The doses used were approximately 1,000 units per pound (2,000 units per kilogram) of body weight, with a maximum dose of 50,000 units. The infant included in this group received 2,000 units per pound (4,000 units per kilogram) because of the variability of breathing pattern in children of this age group.

With the exception of the hood, which can be quickly and easily constructed, all parts are readily obtainable in any hospital. The hood is made of a wire frame covered with washed x-ray film (or plastic material) to give it rigidity. A "vaponefrin" or DeVilbiss no. 40 nebulizer is introduced through an opening at one end of the hood. The flow of oxygen is controlled with a reducing valve and flow meter. Water is supplied to the nebulizer from a continuous drip bottle, the rate of flow being controlled by a simple screw clamp attached to the hood supports

8. Holinger, P.: Acute Laryngotracheobronchitis, Dis. Eye, Ear, Nose & Throat **1**:58-62 (Feb.) 1941. Lederer, F. L.: Diseases of the Ear, Nose and Throat: Principles and Practice of Otorhinolaryngology, ed. 5, Philadelphia, F. A. Davis Company, 1946, p. 684.

and to the rubber tube which conducts water to the nebulizer. The end of this tube is connected with a 20 gage needle, and the needle is then passed through a cork stopper placed in the upper carburetor opening of the nebulizer. If a DeVilbiss nebulizer is used, the needle is placed in the small opening on the side of the chamber.

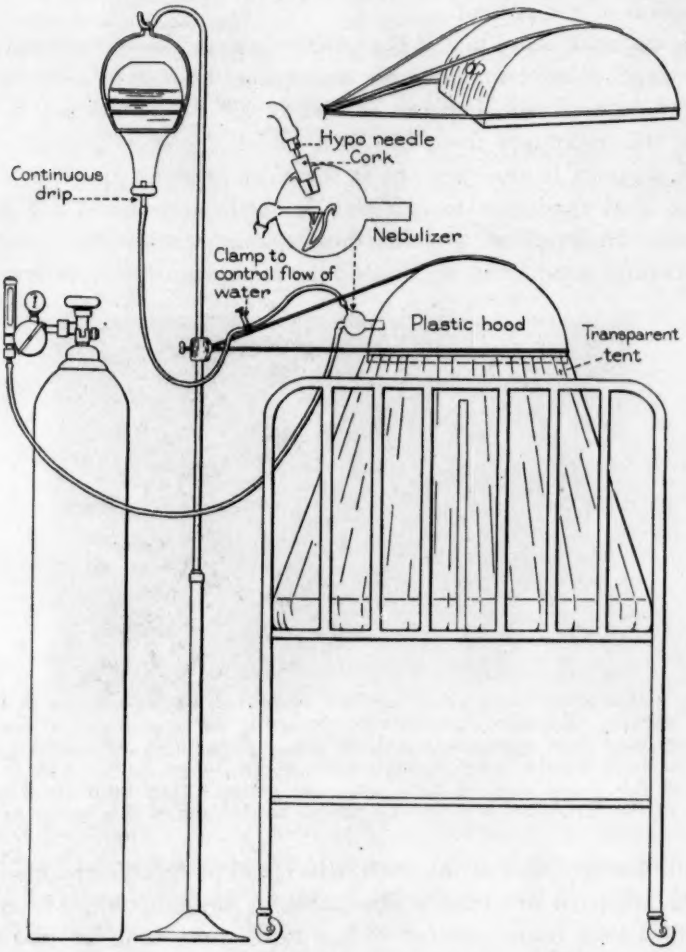

Fig. 4.—Diagrammatic representation of apparatus utilizing a nebulizer for continuous humidification.

The flow of oxygen must be maintained at or above 5 liters per minute to insure adequate humidification and supply of oxygen. Control of temperature depends chiefly on the room temperature. However, the cooling effect of continuous nebulization maintains the temperature inside the tent at a level 3 to 5 degrees (F.) lower than that outside the tent. Additional cooling may be obtained by passing the oxygen through

a coil of rubber tubing 10 to 12 feet (305 to 366 cm.) in length immersed in a bucket of chopped ice.

SUMMARY

1. A new method of administering aerosol penicillin which is applicable to infants and children is described. The apparatus consists of a "vaponefrin" nebulizer and a plastic mask with added inhalation and exhalation valves, forming a closed system. Either a hand bulb or oxygen may be used to produce nebulization.

2. An apparatus to produce high degrees of humidification with use of a nebulizer, plastic hood and canopy is described. The materials for this apparatus (with the exception of the hood) are available in any hospital.

Fig. 5.—Photograph showing a recently tracheotomized infant in an oxygen-humidification tent. A full length midline slide fastener ("zipper") greatly facilitates nursing care.

1819 West Polk Street.

MOTHER-CHILD ABO INCOMPATIBILITY

A Relation of Secretor Status to Mental Deficiency

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MOTHER-CHILD ABO incompatibility occurs in about 20 per cent of all pregnancies.[1] Instances of fetal injury due to ABO maternal isoimmunization, while recognized in increasing numbers,[2] are, however, relatively infrequent. A theoretically protective mechanism was suggested by the observation that in a large majority of persons, the A or the B factor is present in significant concentration in the body fluids.[3] Thus, abnormally stimulated A or B agglutinins transmitted from the mother to the child as a result of isoimmunization could be rapidly neutralized

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From the Southbury Training School and th Department of Pediatrics, Yale Medical School.

1. Levine, P.: Erythroblastosis Fetalis and Other Manifestations of Isoimmunization, West. J. Surg. **50**:468, 1942. Levine observed that in 35 per cent of random matings the blood groups of the mother and father were incompatible. The value of 20 per cent for mother-child incompatibility was derived by excluding those children who might belong to group O.

2. (*a*) Aubert, E. A.; Cochrane, J. B., and Ellis, M. E.: An Unusual Case of Erythroblastosis Fetalis, Brit. M. J. **2**:648, 1945. (*b*) Gruber, S.; Litvak, A., and Jacobi, M.: A Case of Erythroblastosis Fetalis Caused by Isoimmunization with Agglutinogen B, J. Pediat. **29**:518, 1946. (*c*) Hertzog, A. J.: Problems Encountered in Explaining Certain Cases of Erythroblastosis Fetalis on the Rh Theory, Minnesota Med. **26**:1057, 1943. (*d*) Levine, P.; Burnham, L.; Katzin, E. M., and Vogel, P.: The Role of Isoimmunization in the Pathogenesis of Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **42**:925, 1941. (*e*) Polayes, S. H.: Erythroblastosis Fetalis in Mothers with Rh-Positive Blood, Am. J. Dis. Child. **69**:99 (Feb.) 1945. (*f*) Polayes, S. H., and Ohlbaum, C.: Erythroblastosis Fetalis Unrelated to the Rh Factor, Am. J. Clin. Path. **15**:467, 1945. (*g*) Wiener, A. S., and Brody, M.: The Encephalopathy (Kernicterus) of Erythroblastosis Fetalis: Its Serologic Diagnosis and Pathogenesis, Am. J. Ment. Deficiency **51**:1, 1946.

3. Boorman, K. E., and Dodd, B. E.: Group Specific Substances, A, B, M, N, Rh: Their Occurence in Tissues and Body Fluids, J. Path. & Bact. **55**:329, 1943. Wiener, A. S.: Blood Groups and Blood Transfusion, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1929, p. 189 Wiener, A. S., and Belkin, R. B.: Group Specific Substances in the Saliva of the Newborn, J. Immunol. **47**:467, 1943. Levine and others.[2d]

without resulting in tissue damage or destruction of red blood cells. The differentiation of persons normally exhibiting the A or the B factor in their body fluids (secretors) from those in whom the factor is absent or present in relatively insignificant amounts (nonsecretors) was first made by Schiff and Sasaki.[4] Our interest in this aspect of the problem of isoimmunization was further stimulated by the demonstration of cerebral damage (kernicterus) associated with erythroblastosis fetalis resulting from ABO isoimmunization.[2e] Unfortunately, only rarely has the secretor status of the affected child been investigated in these cases.

In a preliminary study,[5] the incidence of mother-child ABO incompatibility associated with nonsecretor status in the child in a group of children with undifferentiated congenital amentia of unknown origin was considerably greater than that in a control group of children with such mental deficiencies as mongolism and postinfectious and post-traumatic defects. In the study, nonsecretor status was established by failure to demonstrate the specific A or B factor in undiluted saliva and gastric juice.

Subsequent studies indicated that utilization of the undiluted saliva and gastric juice for the determination of nonsecretor status was inadequate because of variability on repeated examinations, and that quantitative methods would be necessary to validate the original conclusions.

The purpose of this paper is to report the results of this further study of the possible importance of ABO isoimmunization in the origin of some cases of undifferentiated mental deficiency. Data relative to the problem of secretor status are also included.

SUBJECTS AND METHODS

Subjects.—The subjects were inmates of the Southbury Training School for mentally defective children and were primarily of middle or low grade mental status. The criteria for the selection of children were the availablity of the mother and her willingness to cooperate in having blood studies made. Two hundred and eighty children were included in the study. Their defects were of diverse etiologic categories, which will be described later. The ages of the subjects varied from 6 to 46 years and averaged about 20 years.

Methods.—The presence of the A or the B factor in the saliva was determined as follows: A swab of absorbent cotton was allowed to remain under the tongue until saturated with saliva. This means of obtaining saliva was used because the mental status of most of the children was of too low a grade for them to expectorate on request. The saturated swab was then placed in a small test tube containing 0.2 cc. of isotonic solution of sodium chloride and thoroughly stirred.

4. Schiff, F., and Sasaki, H.: Ueber die Vererbung des serologischen Ausscheidungstypus, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:129, 1932.

5. Yannet, H., and Lieberman, R.: A and B Iso-Immunization as a Possible Factor in the Etiology of Mental Deficiency (Preliminary Report), Am. J. Ment. Deficiency **50**:242, 1945.

About 0.3 cc. of liquid could then be expressed from the cotton tip. The contents of this tube, for the purposes of this study, were considered as the "undiluted" saliva. Serial dilutions, in multiples of 5, were then made by transferring 0.1 cc. of the saliva solution to a test tube containing 0.4 cc. of isotonic solution of sodium chloride and so on, in the usual fashion, the final tube representing a dilution of 1:625. To each tube was added 2 drops of high titer specific anti-A or anti-B human serum, and the tubes were then incubated in the water bath at 37 C. for one hour. Two drops of the specific 2 per cent suspension of washed red blood cells was then added, and the tubes were reincubated for one hour. The tubes were then agitated vigorously and read microscopically.

The gastric juice was obtained in the usual manner with stomach tube and centrifuged; a small amount of the clear supernatant fluid was neutralized with normal sodium hydroxide solution, phenolphthalein being used as indicator. Serial dilutions in multiples of 2 were then made by transferring 0.1 cc. of the neutralized gastric juice to a small test tube containing 0.1 cc. of isotonic solution of sodium chloride and so on, in the usual fashion, the final tube representing a dilution of 1:512. To each tube was added 1 drop of specific anti-A or anti-B human serum.

TABLE 1.—*Results of Repeat Examinations of "Undiluted" Saliva Compared with Original Titers of A and B Agglutinogens in the Saliva*

Original Test Titers	No. of Cases	Repeat Tests on "Undiluted" Saliva		
		Total No. of Tests	No. of Negative Reactions	No. of Positive Reactions
Absent—5	26	52	46	6
25 to 125	14	19	6	13
625 and over	24	38	9	29

The subsequent procedure followed that described previously for saliva. In reading the results for both saliva and gastric juice, the presence of agglutination of red blood cells indicated absence of specific A on B factor in the respective dilution of the test fluid.

RESULTS

The results are presented in such a manner as to indicate the unreliability of the usual method for determining secretor status, namely, the study of a single undiluted specimen of saliva or gastric juice. Table 1 gives a summary of the results for saliva. Of 52 tests with undiluted saliva studied at various times over a period of one year on 26 persons in whom original quantitative studies indicated either the absence of specific factor or its presence in titers of less than 25, the vast majority (88 per cent) gave negative results. Of 19 repeated tests on the undiluted saliva of 14 persons in whom the original study indicated the presence of specific factor in titers of 25 but less than 625, negative results were obtained in 32 per cent. Even in the 24 persons whose titers of specific factor were at least 625, about 24 per cent of the 38 repeat tests on the undiluted

saliva gave negative results. Thus, it appears that a single examination of undiluted saliva is of limited value as an indication of secretor status.

Table 2 gives a summary of a similar analysis of the results for gastric juice. Of 24 repeat tests on undiluted gastric juice of 17 persons in whom the original quantitative study indicated either absence of specific factor or its presence in titers of less than 16, 88 per cent gave negative results. In 12 repeat tests on 12 persons with titers of specific factor of 16 or more, there were no negative reactions. Thus, as regards gastric

TABLE 2.—*Results of Repeat Examination of "Undiluted" Gastric Juice Compared with Original Titer of A and B Agglutinogens*

Original Test Titers	Number of Cases	Repeat Tests on "Undiluted" Gastric Juice		
		Total No. of Tests	No. of Negative Reactions	No. of Positive Reactions
Absent to 8	17	24	21	3
16 to 256	6	6	0	6
512 and over	6	6	0	6

TABLE 3.—*Correlation Between A and B Agglutinogen Titers for Saliva and for Gastric Juice in 38 Cases*

Titers for Saliva	Titers for Gastric Juice			
	Absent	2 to 8	16 to 256	512 and over
Absent	10	9	3	1
5		1		
25 to 125			2	2
625 and over			4	6

juice, while a single negative reaction to a test on undiluted fluid is probably significant, a positive result needs further verification.

Table 3 shows the correlation between the titers of specific factors for saliva and the titers for gastric juice obtained at the same time for 38 persons. A definite positive relation is apparent. Thus, of the 20 children for whom the specific factor in the gastric juice was either absent or present in titers of less than 16, all but 1 showed absence of specific factors in the saliva, and in this 1 child the salivary titer was less than 25. All titers for the saliva of 25 or greater were associated with titers of 16 or greater for the gastric juice.

It is apparent that the concept of secretor status must be considered a relative one. Therefore, for the purpose of our study, we designated a subject as a nonsecretor if the specific A or B factor was either absent in both saliva and gastric juice or present in a titer of less than 25 in saliva and of less than 16 in the gastric juice. Of the total of 280 inmates studied, 20 were encountered whose blood types were incompatible with that of their mothers and who fitted our definition of nonsecretors. Their distribution according to the diagnostic classification of their defects is given in table 4.

It will be noted that of the total group 157 patients could be classified under specific diagnostic categories. The incidence of mother-child AB incompatibility in these groups varied from 13 to 24 per cent, with an average of 20 per cent. This average is well within the expected value for the general population. These patients may be considered the control

TABLE 4.—*Distribution of Inmates According to Mother-Child Incompatibility and Presence of Nonsecretor Status in Child*

Diagnostic Classification	Number with Defect	Mother-Child Incompatibility		Nonsecretor Status in Child	
		No.	%	No.	%
Mongolism	46	11	24	2	4
Spastic diplegia	33	6	18	1	3
Familial defect	22	4	18	1	5
Postinfectious deficiency	22	4	18	0	
Post-traumatic deficiency	17	3	18	0	
Craniofacial defect	9	2	22	0	
Miscellaneous defects	8	1	13	0	
Total (control) known defects	157	32	20	4	3
Undifferentiated defects	123	38	31	16	13

group. The 123 children whose defects were diagnosed as "undifferentiated" represented congenital amentia for which complete medical, laboratory and social service studies failed to reveal any known etiologic or diagnostic factors. The incidence of mother-child AB incompatibility for this group was 31 per cent, a value significantly greater than for the control group. Of the 20 persons in the total study who, in addition to showing incompatibility, were found also to be nonsecretors, 4 (3 per cent) were in the control group and 16 (13 per cent) in the undifferentiated group. Expressed in another way, of the children with AB incompatibility in the control group, 12.5 per cent were also nonsecretors, as compared with 42 per cent in the undifferentiated group. These differences between the control and the undifferentiated group are significant satistically and lead to the conclusion that in at least some of the cases of deficiencies now diagnosed as undifferentiated the possibility

exists that the cerebral maldevelopment was related to maternal ABO isoimmunization.

COMMENT

The results indicate the variable nature of the secretor status. Single tests on undiluted saliva or gastric juice appear to be of limited diagnostic value in this respect. This limitation is particularly apparent when saliva alone is analyzed. At different times for the same person, it is possible to show either complete absence of the specific agglutinogen or its presence in variable quantities. A more consistent picture is obtained when both gastric juice and saliva are simultaneously examined and titered. Whether we are justified in considering as nonsecretors those persons with relatively small concentrations of specific agglutinogen in the saliva and gastric juice is not entirely clear. Further studies are necessary to clarify that point completely. However, for the purpose of the present comparative study, the arbitrary definition selected seemed desirable.

There is little definite knowledge of the clinical applications of the concept of secretor status. In the few reported cases of erythroblastosis fetalis associated with ABO isoimmunization, adequate studies of specific A or B factors in the body fluids of the child were not carried out. The present study represents an indirect approach to this problem, which will need confirmation by other lines of investigation.

A clinical review of the 16 children with undifferentiated deficiencies who exhibited ABO maternal incompatibility and who probably were also of nonsecretor status is of considerable interest. Theoretically, this group probably includes some children with cerebral damage due to maternal AB isoimmunization. The findings can be summarized briefly as follows:

The histories revealed 2 instances of unexplained stillbirths in one family and 1 instance in another. In one family, a sibling was recorded as a congenital deaf-mute. The average maternal age at the birth of the children was 27.1 years. This age is close to the expected maternal age (27.3) for all children born in Connecticut in 1925, the average year of birth of the children in this group. Murphy[6] pointed out the importance of advanced maternal age as an etiologic factor in congenital developmental anomalies, and the absence of this factor in the group is of some slight negative importance. The average circumference of the heads of the children in the group was 52.2 cm., which is not abnormal. Convulsive disorders were present in 7 of the 16 children. This finding is probably not significant, since among the children with low and middle

6. Murphy, D. P.: Congential Malformations, Philadelphia, University of Pennsylvania Press, 1940.

grade deficiencies in the general instiutional population the incidence of convulsive disorders may be as high as 20 per cent.[7] For a similar reason, the occurrence of 2 instances of extracerebral congenital anomalies in the group is probably of no significance. The neurologic findings were in no way characteristically different from those obtained in the majority of children with middle and low grade mental deficiencies in the undifferentiated category. As a rule, the deep reflexes were somewhat hyperactive but equal on the two sides; the Babinski responses were usually flexor, and the muscular tone was normal or slightly increased. The sensory status, when cooperation could be obtained, was as a rule within normal limits, and the fundi showed nothing unusual. The average mental age of the group was represented by an intelligence quotient of approximately 30. Since the studies were carried out primarily on children with deficiencies in the low and middle grade categories, this observation is of no significance Similar studies among children with undifferentiated deficiencies of moron category are obviously needed.

Seven (44 per cent) of the 16 children with AB incompatibility and undifferentiated deficiencies were first born. This incidence may be compared with the value of 36 per cent representing the proportion of all children born in 1925 in Connecticut who were first born. The difference is not significant. The occurrence of erythroblastosis fetalis due to Rh isoimmunization is almost exclusively confined to children born of a second or later pregnancy, and only in rare instances in the first-born child effected. A normal proportion of first-born children in our group is, therefore, of importance. Of significance in connection with the previous observation is the fact that in not a single instance could a neonatal history be obtained which might be compatible with, or even suggestive of, a diagnosis of erythroblastosis fetalis. This situation is strikingly different from that in the reported cases of cerebral damage due to Rh isoimmunization, in the majority of which the neonatal occurrence of erythroblastosis fetalis was unmistakable, even though the history was obtained from the parents many years after the birth of the child.[8]

If our statistical data are valid, it must be assumed that the pathogenesis of injury due to ABO isoimmunization under certain conditions may be fundamentally different from that usually operating in Rh isoimmunization. Unfortunately, studies of ABO isoimmunization have been confined primarily to infants exhibiting symptoms suggestive of the erythroblastosis fetalis syndrome when the mother is demonstrated to be

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7. Yannet, H.: Diagnostic Classification of Patients with Mental Deficiency, Am. J. Dis. Child. **70**:83 (Aug.) 1945.

8. Vaughn, V. C.: Kernicterus in Erythroblastosis Fetalis, J. Pediat. **29**: 462, 1946. Yannet, H., and Lieberman, R.: Central Nervous System Complications Associated with Kernicterus, J. A. M. A. **130**:335 (Feb. 9) 1946.

Rh positive. The possibility that serious cerebral damage may occur as a result of ABO isoimmunization without significantly involving the blood or the other organ systems, as is usually the case in Rh isoimmunization, is strongly suggested by the data.

SUMMARY

A total of 280 children with moderate or severe mental deficiencies was studied to determine the incidence of mother-child ABO incompatibility. Of these, 157 represented clinical examples of well recognized diagnostic categories, such as mongolism, congenital spastic diplegia and postinfectious and post-traumatic defects. The children with these defects were considered as the control group. The deficiencies of the remaining 123 children were of the undifferentiated type, ordinarily diagnosed as congenital amentia of unknown origin. A total of 20 children were found who, in addition to ABO maternal incompatibility showed absence or relatively minor concentrations of the A or the B factor in the saliva and the gastric juice (i.e., a nonsecretor status). A significantly greater proportion of incompatible nonsecretors was found in the group with undifferentiated defects (13 per cent) than in the control group (3 per cent). This incidence was interpreted as indicating the possibility of ABO isoimmunization as the etiologic factor in a small number of children with undifferentiated congenital deficiencies.

Clinical evaluation of these cases reveals striking differences from the clinical picture usually associated with cerebral damage due to Rh isoimmunization. These differences include a higher incidence of first-born children, absence of a neonatal history suggesting erythroblastosis fetalis and absence of gross motor defects.

If the data are valid, it must be concluded that fundamental differences may exist in the pathogenesis of cerebral injury due to Rh incompatibility and that due to ABO isoimmunization.

Southbury Training School.

VITAMIN A, CAROTENE AND ASCORBIC ACID CONTENT OF NURSERY SCHOOL LUNCHES

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ALL OF the studies which have been made to determine the ascorbic acid requirement of preschool age children produced similar results. Everson and Daniels[1] observed that the retention of ascorbic acid paralleled the ingestion only up to about 7.5 mg. per kilogram of body weight for 3 boys, 39, 57 and 59 months of age. Hathaway and Meyer[2] concluded that 31 mg. of ascorbic acid was the marginal level to insure tissue saturation and that utilization was relatively constant at levels of intake from 31 to 53 mg. per day, while Bessey and White[3] reported that 80 per cent of the 93 children studied, who were between 5 and 13 years, maintained blood plasma levels indicative of liberal intake when they received 3 ounces (about 85.35 Gm.) of orange juice (45 mg. of abscorbic acid) per day. In accordance with these results, the National Research Council's[4] recommended daily allowances are 35 mg. for 1 to 3 year old children and 50 mg. for 4 to 6 year old children. Consequently, it is assumed that the midmorning lunch and the noon meal at the nursery school should contribute at least 50 per cent of the child's ascorbic acid requirement, namely 17.5 and 25 mg. for the younger and the older groups respectively.

The data for this paper taken from a thesis submitted in partial fulfilment of the requirements for the degree of Master of Science.

1. Everson, G. J., and Daniels, A. L.: Vitamin C Studies with Children of Preschool Age, J. Nutrition **12**:15-25, 1936.

2. Hathaway, M., and Meyer, F.: Studies of Vitamin C Metabolism of Four Preschool Age Children, J. Nutrition **21**:503-514, 1941.

3. Bessey, O. A., and White, R. L.: The Ascorbic Acid Requirements of Children, J. Nutrition **23**:195-203, 1942.

4. Recommended Allowances of Various Dietary Essentials, Food and Nutrition Board, National Research Council, Reprint and Circular Series, no. 122, Washington, D. C., 1945, p. 10.

TABLE 1.—*Ascorbic Acid Content of Nursery School Lunches During a Ten Day Period*

Date	Milligrams of Ascorbic Acid in Composite Food Samples* and in Milk†																	
	Food Composite			Milk			Total			Food Composite			Milk			Total		
	Reduced	Dehydro-ascorbic acid‡	Total	Reduced	Dehydro-ascorbic acid‡	Total	Reduced	Dehydro-ascorbic acid‡	Total	Reduced	Dehydro-ascorbic acid‡	Total	Reduced	Dehydro-ascorbic acid‡	Total	Reduced	Dehydro-ascorbic acid‡	Total
	Older Group									Younger Group								
(July) 14	0.00	45.66	45.66	0.82	3.22	4.04	0.82	48.88	49.70	0.00	44.76	44.76	0.82	3.22	4.04	0.82	47.98	48.80§
15	2.71	39.91	42.62	0.82	3.22	4.04	3.53	43.14	46.66	2.83	37.28	40.11	0.82	3.22	4.04	3.65	40.50	44.15§
22	0.00	62.51	62.51	0.82	3.22	4.04	0.82	65.73	66.55	0.00	56.15	56.15	0.82	3.22	4.04	0.82	59.37	60.19
23	5.77	59.70	65.47	0.82	3.22	4.04	6.59	61.92	69.51	4.85	53.65	58.50	0.82	3.22	4.04	5.67	56.87	62.54
24	0.94	39.12	40.06	0.82	3.22	4.04	1.76	42.34	44.10	0.30	39.50	39.80	0.82	3.22	4.04	1.12	42.72	43.84
25	10.68	45.19	55.87	0.54	3.30	3.84	11.22	48.49	59.72	5.11	28.34	33.45	0.54	3.30	3.84	5.65	31.64	37.30§
26	2.84	71.11	73.95	0.54	3.30	3.84	3.38	74.41	77.80	2.15	67.65	69.80	0.54	3.30	3.84	2.69	70.95	73.65§
29	0.54	69.37	69.91	0.54	3.30	3.84	1.08	72.67	73.76	0.50	51.30	51.80	0.54	3.30	3.84	1.04	54.60	55.65§
30	1.18	46.40	47.58	0.54	3.30	3.84	1.72	49.70	51.43	0.97	44.65	45.62	0.54	3.30	3.84	1.51	47.95	49.47§
31	1.09	54.28	55.37	0.54	3.30	3.84	1.63	57.58	59.22	1.04	52.37	53.41	0.54	3.30	3.84	1.58	55.67	57.26§
Average	2.58	53.32	55.90	0.68	3.26	3.94	3.25	56.48	59.84	1.77	47.57	49.34	0.68	3.26	2.94	2.45	50.83	53.28

*Includes midmorning tomato juice.
†The values for milk were determined in two five day composite samples, the first five day period from July 14 through July 24, and the second five day period from July 25 through July 31.
‡Obtained by subtracting the amount of reduced ascorbic acid from the total.
§The composite food samples of the younger group of children varied less than plus or minus 10 per cent in weight from those of the older group.

Similar data on the vitamin A requirement of preschool age children is not available. Although Hess, Lewis and Barenberg[5] stated that the demand for vitamin A is greater during early childhood, they expressed the belief that the usual diet meets the child's needs except when vagaries of diet occur or absorption is deficient, as in diarrhea and jaundice. The National Research Council's[4] daily dietary recommendations are 2,000 international units for children 1 to 3 years old and 2,500 international units for children 4 to 6 years old.

The present study was undertaken to determine the quantity of vitamin A and carotene and total and reduced ascorbic acid in the midmorning lunch and noon meal served nursery school children.

PROCEDURE

The midmorning lunch and the noon meal served the 2½ to 5 year old children in the North Texas State College Nursery School were analyzed for ten consecutive days during the summer of 1947. The amount of food served each child varied with his age group. There were two age groups: the younger ranged from 2½ to 3½ years and the older from 3½ to 5 years. Consequently, duplicate servings of each food served each age group were collected for analysis on each of the ten days.

"Ball eclipse" wide mouth jars containing 100 cc. of 1 per cent metaphosphoric acid were used for the collection of the food from each meal of each age group. The midmorning tomato juice served to each age group was added to the appropriate lunch. The milk was analyzed separately as 2 five day composite samples.

The procedures used in determining the reduced content of ascorbic acid and the vitamin A and carotene of the foods were identical with those reported by Scoular and Kelsay.[6] In addition, the total content of ascorbic acid was determined, using Roe and Osterling's[7] modification of Roe and Kuether's[8] method. The dehydroascorbic acid was then calculated by substracting the reduced from the total value.

COMMENT

Total ascorbic acid and values for dehydroascorbic acid and reduced ascorbic acid were determined for a ten day period on composite food samples and on composite milk samples served the 16 children attending the North Texas State College Nursery School. These children were divided into two groups for serving, the older and the younger. The ages

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5. Hess, A. F.; Lewis, J. M., and Barenberg, L. H.: Does Our Dietary Need Vitamin A Supplement? J.A.M.A. **101**:657-663 (Aug. 26) 1933.

6. Scoular, F. I., and Kelsay, J.: Reduced Ascorbic Acid, Carotene and Preformed Vitamin A of Dormitory Foods, J. Am. Dietet. A., to be published.

7. Roe, J. H., and Oesterling, J.: Determination of Dehydroascorbic Acid and Ascorbic Acid in Plant Tissues by the 2,4-Dinitrophenylhydrazine Method, J. Biol. Chem. **152**:511-517, 1944.

8. Roe, J. H., and Kuether, C. A.: Determination of Ascorbic Acid in Whole Blood and Urine Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, J. Biol. Chem. **147**:399-407, 1943.

of the children in the former group ranged from 42 to 54 months and in the latter group from 30 to 36 months.

Only three of the day's composite food samples, containing the mid-morning tomato juice served to each of these groups, varied more than plus or minus 10 per cent in weight during the ten day period. As a result, the average daily values for total ascorbic acid, reduced ascorbic acid and dehydroascorbic acid (table 1) for the older and younger groups did not vary greatly—59.8, 3.3 and 56.5 and 53.3, 2.5 and 50.8 mg., respectively. A similar relationship exists between the ranges of values for each form of ascorbic acid determined. The range for total ascorbic acid was 44.1 to 77.8 mg. for the older group and 37.3 to 73.7 mg. for the younger, while the reduced value varied from 0.82 to 11.2 and 0.82 to 5.7 mg. for the older and younger groups, respectively. The dehydroascorbic acid ranges were greater than the reduced ranges, but similar to those obtained for total ascorbic acid, namely, 42.3 to 74.4 mg. for the older and 31.6 to 70.9 mg. for the younger children. This represented from 94 to 96 per cent of the total dehydroascorbic acid. McMillan and Todhunter[9] observed from 19 to 45 per cent in this form. These authors also reported 68 per cent of the ascorbic acid in milk occurred as dehydroascorbic acid, whereas 82 per cent was obtained in the present study.

For both groups of children, the highest total ascorbic acid was obtained on those days when the menu served contained either a citrus fruit, cabbage slaw or fresh vegetable salad containing raw tomato. The highest total ascorbic acid, 77.8 mg. for the older group and 73.6 for the younger group, was obtained on the day when raw cabbage was served. The second highest, 69.5 and 62.5 mg., was observed on the day when orange and pineapple compote was served for dessert, whereas the lowest values resulted for the older group with a lunch containing tomato and cheese soufflé, stewed prunes, vegetable salad, orange toast, oatmeat cookies and milk. The younger group's lowest intake occurred when the menu consisted of baked fish, parsley potatoes, green beans, fruit salad (no oranges), toast and milk. Both Scoular and Bryan[10] and McMillan and Todhunter[9] analyzed school lunches for ascorbic acid and reported that each of the menus which provided the highest values of ascorbic acid included some citrus fruit.

According to the National Research Council's[4] recommended allowances 50 mg. of ascorbic acid per day will suffice for children from 4 to 6 years of age. On all but three days, the total ascorbic acid intake of the older group was higher than this recommended allowance. Conse-

9. McMillan, T. J., and Todhunter, E. N.: Ascorbic Acid Content of School Lunches, J. Am. Dietet. A. **22**:404-407, 1946.

10. Scoular, F. I., and Bryan, A. R.: Ascorbic Acid Content of School Lunches, J. Home Econ. **36**:651-655, 1944.

quently, only on days when the lunches furnished 44.1, 46.7 and 49.7 mg., respectively, did the diets of these children require additional ascorbic acid, other than that provided by the midmorning tomato juice and the noon meal. The minimum intake for the younger children was 37.3 mg. Since all of the nursery school lunches exceeded the National Research Council's[4] recommended 35 mg. for the 1 to 3 year age group, the ascorbic acid in the food eaten at home gave them a more optimum intake than that of the older group.

During the entire period of analysis the food served at the nursery school to both groups of children met the 31 mg. requirement, which Hathaway and Meyer[2] observed to be the marginal level to insure tissue saturation in preschool age children.

The average body weight of the older group of children studied was 16.2 Kg. and of the younger group, 14.1 Kg. The total ascorbic acid obtained from the food served in the present study gave an average of 3.7 mg. ascorbic acid per kilogram of body weight for the older group of children and 3.8 mg. for the younger children. These values are lower than the 7.5 mg. per kilogram of body weight which Everson and Daniels[1] observed to be the upper limit at which retention paralleled intake.

It is apparent from these comparisons that the nursery school lunches with the midmorning tomato juice supplied an ample amount of ascorbic acid. The nursery school lunches are planned to supplement, not replace, the foods eaten at home.

Vitamin A and carotene were determined on the same composite food samples, containing the midmorning tomato juice, and on the five day composite milk samples which were analyzed for ascorbic acid and previously reported herein.

As previously stated, only three of the day's composite food samples, containing the tomato juice served each of these groups of children, varied more than plus or minus 10 per cent in weight during the entire period. Consequently, the average daily vitamin A and carotene and average total vitamin A value (table 2) for the older and younger children showed little variance. To illustrate, the average values for vitamin A were 6,576 and 1,559 and for carotene 6,487 and 1,342 international units for the older and younger groups, respectively. The total vitamin A was obtained by adding 75 per cent of the carotene to the vitamin A, because Lesher, Brody, Williams and Macy[11] calculated carotene to have vitamin A activity equivalent to 75 per cent of that of pure beta carotene. The total vitamin A of the present food composites averaged 7,736 international units for the older group and 7,483 for the younger group.

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TABLE 2.—*Vitamin A and Carotene Content of Nursery School Lunches During a Ten Day Period of Analysis*

Date	International Units Vitamin A and Carotene in Composite Food Samples* and in Milk†																	
	Food Composite			Milk			Total			Food Composite			Milk			Total		
	Vitamin A	Carotene	Total‡	Vitamin A	Carotene	Total‡	Vitamin A	Carotene	Total‡	Vitamin A	Carotene	Total‡	Vitamin A	Carotene	Total‡	Vitamin A	Carotene	Total‡
	Older Group§									Younger Group								
July 14[4]	5,112	2,614	7,822	865	0	865	5,977	3,614	8,687	5,112	3,614	7,822	865	0	865	5,977	3,614	8,687
15[4]	1,674	1,611	2,882	865	0	865	2,539	1,611	3.747	1,674	1,611	2,882	865	0	865	2,539	1,611	3,747
22	3,227	3,100	5,552	865	0	865	4,092	3,100	6,417	3,309	1,504	4,437	865	0	865	4,174	1,504	5,302
23	3,686	2,171	5,314	865	0	865	4,551	2,171	6,179	3,404	1,712	4,688	865	0	865	4,269	1,712	5,553
24	7,119	1,271	8,072	865	0	865	7,984	1,271	8,937	6,430	1,149	7,292	865	0	865	7,295	1,149	8,157
25[4]	2,345	565	2,769	861	0	861	3,206	565	3,630	2,345	565	2,769	861	0	861	3,206	565	3,630
26[4]	3,765	897	4,338	861	0	861	4,626	897	5,199	3,765	897	4,338	861	0	861	4,626	897	5,199
29[4]	6,265	283	6,478	861	0	861	7,126	283	7,339	6,265	283	6,478	861	0	861	7,126	283	7,339
30[4]	10,635	1,194	11,531	861	0	861	11,497	1,194	12,392	10,635	1,194	11,531	861	0	861	11,497	1,194	12,392
31[4]	21,932	890	22,599	861	0	861	22,793	890	23,460	21,932	890	22,599	861	0	861	22,793	890	23,460
Average	6,576	1,559	7,736	863	0	863	7,439	1,559	8,598	6,487	1,342	7,483	863	0	863	7,350	1,342	8,346

*Includes midmorning tomato juice.
†The values for milk were determined in two five day composite samples, the first five day period from July 14 through July 24, and the second five day period from July 25 through July 31.
‡Total vitamin A values were obtained by adding 75 per cent of carotene value to vitamin A.
§Composite samples of these days did not vary in total weight more than plus or minus 10 per cent. The average weight of the daily food composites served the older group was 367 Gm. and for the younger group, 350 Gm. Therefore, the latter were not analyzed separately for these days.

No carotene was observed in the milk samples, while the average vitamin A was 863 international units. This value is higher than that (750 international units) obtained by others in our laboratory from the same milk source. This difference may be attributed to the season of the year. The earlier average was obtained in December through May and the present one in July.

The highest total vitamin A value, 23,460 international units in the food composite plus milk for each group was obtained on the day when the menu consisted of scrambled eggs, baked potatoes, vegetable salad, bacon sandwiches, ice cream (made partly with evaporated milk) and milk. The second highest value, 12,392 international units, was observed on the day when the menu included broiled liver, buttered broccoli, potato salad, cinnamon toast, fruit compote and milk. One might have expected a higher value to result from this menu than from the one previously described; however, it must be emphasized that the servings of liver and broccoli which are exceptionally high in vitamin A, were small.

The highest value for carotene, 3,614 international units, for the two groups, was obtained from the menu containing cheese croquettes, harvard beets, baked potatoes, cabbage slaw, toast, banana and milk. The following menu, deviled eggs, English peas, buttered cauliflower, carrot and raisin salad, toast, banana and milk, gave the second highest amount of carotene, 3,100 international units, in the food served the older group. A second high carotene value, 1,712 international units, for the younger group, resulted when broiled liver, buttered spinach, scalloped potatoes, carrot sticks, orange and pinapple compote, toast and milk were served.

The lowest vitamin A value, 3,630 international units, for both groups, was obtained from a menu containing baked fish, tomato sauce, parsley potatoes, green beans, fruit salad, toast and milk. The lowest value for carotene, 283 international units, resulted from the following menu: English peas, deviled egg salad, diced tomatoes, buttered cauliflower, toast, banana and milk.

The composite food served the older group of children contained 85 per cent of preformed vitamin A and 15 per cent of carotene, whereas that of the younger group had 87 per cent of preformed vitamin A and 13 of carotene. All of the milk samples were 100 per cent vitamin A.

The National Research Council[4] recommends 2,500 international units of vitamin A for children from 4 to 6 years of age and 2,000 for those from 1 to 3 years of age. This study reports total vitamin A values which greatly exceed these recommendations, although the food represents only the noon meal and the midmorning tomato juice served the children at the nursery school.

Although each child except 1 ate all of the aforementioned foods served his age group on each of the ten days of this study, many of the

children also had second servings of food, none of which were included in the reported values for the day. It is evident that they were not needed to improve the content of ascorbic acid, vitamin A and carotene of these lunches. All of the lunches supplied an excess of vitamin A and carotene for each age group. This might also be said of the ascorbic acid, although these amounts were not as great as the total amount of vitamin A. It is concluded from this study of these two vitamins that children's needs are amply supplied by these nursery school lunches.

SUMMARY

The total ascorbic acid content of all the noon meals plus the tomato juice exceeded one half of the child's daily requirement. All of the foods served each group on the days studied meet the total daily requirement except for three days' food served the older group.

The preformed vitamin A alone obtained in the nursery school food provided from two to three times the recommended daily allowance, while the carotene supplied an additional amount not included in the preformed vitamin A.

All of the 16 children with the exception of 1 child ate all of the food served on the days of this study. All of the other children had one or more "seconds." It is concluded that the nursery school food analyzed provided vitamin A, carotene and total ascorbic acid in excess of that necessary in one meal, even when that meal is the noon meal of the day.

POSSIBLE DISSEMINATION OF POLIOMYELITIS VIRUS BY CARRIERS

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IN A PREVIOUS communication[1] it was suggested that foods may play a role in the dissemination of the virus of poliomyelitis. Experimental evidence that flies may contaminate food was suggested by Ward, Melnick and Horstmann.[2] Recent observations by Melnick and Penner[3] have shown that a human strain of the virus of poliomyelitis may be recovered from excreta of fed flies for as long as three weeks.

In this work it was thought that means other than flies may possibly play a role in contaminating fresh foods with virus.

MATERIALS AND METHODS

Collections of stools were begun from 5 peddlers who delivered fresh fruits and vegetables from house to house in and around Salt Lake City. After the first two samples of stool were collected, 2 of these peddlers moved from the area. Three of the peddlers continued to work in the area chosen for the experimental work. From each man, two stool samples were collected each month for nearly a year. Collected samples were processed and tested for virus by injection into monkeys.

Various kinds of fruit were collected from several sources, including fruits from delivery trucks of different peddlers.

Stool Specimens.—When monkeys were available, specimens of stool were processed within a week or two after collection. They were stored in a carbon dioxide freezer until processed. It was necessary to store some of the samples three or four months before testing, owing to the shortage of monkeys.

About 5 Gm. of stool was ground and diluted with 20 to 30 cc. of isotonic solution of sodium chloride. This mixture was then centrifuged and the supernatant treated for eighteen to twenty-four hours with ether. The volume was then reduced in a lyophil apparatus to from 5 to 10 cc. Monkeys were given in-

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

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2. Ward, R.; Melnick, J. L., and Horstmann, D.: Poliomyelitis Virus in Fly-Contaminated Food Collected at an Epidemic, Science **101**:491-493, 1945.

3. Melnick, J. L., and Penner, L. R.: Experimental Infection of Flies with Human Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **65**:342-346, 1947.

jections intracerebrally, intranasally and intraperitoneally, the total volume of the processed sample being used.

Fruit Specimens.—Samples of fruit were washed with a secondary fifteenth-molar phosphate solution, p_H 8.2 to 8.4, a rubber policeman being used to scrub the surface of the fruit thoroughly. Usually 20 to 30 cc. of solution was required to wash twelve to twenty-four pieces of fruit. Previous experiments conducted with

TABLE 1.—*Results of Examinations of Fruit Peddlers' Stools for the Virus of Poliomyelitis*

Experiment No.	Stool Sample Collected	Monkey Inoculated with Processed Stool; Injections	Results
1	June and July, 1946: T.B., E.N., J.B.; tested in July	Macaca mulatta: Pooled stool injected: 4 injections 0.5 cc. I.C.* and 4 injections 0.5 cc. nasally; 1 injection 10 cc. I.P.*	Monkey nervous 7 to 8 days; no paralysis; killed on 19th day; histologic sections showed typical poliomyelitis
2	June: T.B.; stored 4 months	Macaca mulatta: 5 injections I.C.; 5 injections S.C.,* and 5 injections nasally on successive days	No poliomyelitis
3	June; E.N.; stored 4 months	Macaca mulatta: 5 injections I.C.; 5 injections S.C., and 5 injections nasally	No poliomyelitis
4	July: J.B.; stored 3 months	Macaca mulatta: 5 injections I.C.; 5 injections S.C., and 5 injections nasally	No poliomyelitis
5	July, Aug. and Sept.: T.B., E.N.; tested in Sept.	Macaca mulatta: Pooled stool of 6 collections; injected 4 successive days I.C., nasally and S.C.	Monkey died 6th day; no pathologic evidence of poliomyelitis
6	Jan. and Feb. 1947: T.B.; tested in March	African green monkey: Three samples pooled; 4 injections I.C.; 2 injections nasally, and 1 injection I.P. of 5 cc.	Monkey had pronounced tremors, paralysis of both legs, arms weak; histologic section showed poliomyelitis
7	Jan. and Feb.: J.B.; tested in March	African green monkey: 3 injections I.C. and 1 injection nasally	No poliomyelitis
8	June and July: T.B.; stored 10 months	Cynomolgus: Pool of 2 months' collection processed; 0.5 cc. I.C. and 0.5 cc. nasally 4 times	No poliomyelitis
9	Aug. and Sept.: T.B.; stored 8 months	Cynomolgus: Pooled 2 mo. collection processed; 4 injections I.C. and 4 injections nasally	No poliomyelitis
10	Feb. and March: T.B.; tested in May	Cynomolgus: Pooled 2 mo. samples processed; 4 injections I.C. and 4 injections nasally	No poliomyelitis
11	April: T.B.; tested in May	Cynomolgus: Pooled 1 mo. sample processed; 4 injections I.C. and 4 injections nasally	Monkey died 24th day; no pathologic evidence of poliomyelitis

*I.C. signifies injection was given intracerebrally; I.P., that it was given intraperitoneally and S.C., that it was given subcutaneously.

the M-H (mouse hamster) virus showed that this method recovered all virus artifically placed on fruit. Immediately after the washing the p_H of the wash fluid was reduced to from 6.5 to 7 by the addition of dilute hydrochloric acid, then the fluid was reduced in volume in the lyophil apparatus to from 5 to 10 cc. All the wash fluid was injected into monkeys. In one experiment, fruit peelings were ground and the fluid was processed and injected.

In all cases in which signs of poliomyelitis failed to develop in the monkeys, they were killed thirty to forty days after inoculation, and histologic sections were examined for lesions of poliomyelitis.

RESULTS

Samples of Stools from Fruit Peddlers.—Table 1 shows results of these experiments. Owing to the shortage of monkeys, pooled samples of stool were processed in some of the experiments. Collections were made in June and July (1946), and the resulting processed sample of the stools of T.B., E.N. and J.B. was injected into a monkey in the latter part of

TABLE 2.—*Results of Testing Fruit for the Presence of the Virus of Poliomyelitis*

Sample No.	Source of Samples	Types of Samples	Animal: Injection	Poliomyelitis
1	Three fly traps in 3 epidemic cities; fruit fallen to ground near home of poliomyelitis patient (Aug. to Sept.)	Peach, plum, pear peelings and washings (pooled 4 samples)	Macaca mulatta: 0.5 cc. I.C.* on 5 successive days plus 10 cc. I.P.*	Negative
2	Pooled banana from 6 fly traps set near homes of poliomyelitis patients (Aug. to Sept.)	Banana, 6 samples (pooled sample)	Macaca mulatta: 0.5 cc. I.C. on 5 successive days plus 5 cc. I.P. on two days	Negative
3	Pooled banana from 5 fly traps set in two small towns in which poliomyelitis was epidemic (Aug. to Sept.)	Banana, 15 samples (pooled sample)	Macaca mulatta: 0.5 cc. I.C. on 5 successive days plus 5 to 8 cc. I.P. for 5 days	Negative
4	Fruit from peddler's truck (Aug.—J.W.)	Peach and pear (pooled sample)	Macaca mulatta: 0.5 cc. I.C. for 4 successive days; 0.5 cc. nasally 3 days	Negative
5	Fruit from peddler's truck (S.P.S.—Sept.)	Peach and plum (pooled sample)	African green monkey: 0.5 cc. I.C. 4 times; 0.5 cc. nasally 4 times	Negative
6	Fruit from fruit peddler's truck (T.B.—Sept.)	Peach and apple (pooled sample)	African green monkey: 0.5 cc. I.C. and 0.5 cc. nasally on 4 successive days	Negative
7	Fruit peddler's truck (E.N.—Aug.)	Peach and pear (pooled sample)	African green monkey: 0.5 cc. I.C. and 0.5 cc. nasally on 4 successive days	Negative
8	Fruit peddler's truck (H.W.—Jan.)	Apple (pooled sample)	African green monkey: 0.5 cc. I.C. and 0.5 cc. nasally on 4 successive days	Negative
9	Fruit orchard ¼ mile from family with 3 poliomyelitis patients (Sept.)	Apple and pear (pooled sample)	Macaca mulatta: 1 cc. I.C. plus 10 cc. I.P. Cotton rat: 0.1 cc. I.C. and 0.2 cc. I.P. 2 mice: 0.03 cc. I.C.	Negative
10	Fruit collected Aug., Sept., Oct. and Jan.	Pooled apple, pear, plum, banana, peach	Cynomolgus: 0.5 cc. I.C. 4 days; 0.5. cc. nasally 3 days	Negative

*I.C. indicates injection was given intracerebrally, while I.P. designates an intraperitoneal injection.

July. Virus was isolated from this pool. Subsequent samples failed to reveal virus. Another test on the June and July collections was carried out on the stool from T.B. in May 1947, using Cynomologus monkeys, but no virus was found. The long storage in carbon dioxide may have destroyed the virus.

Because of the shortage of monkeys, the October-November-December samples were not tested.

The January-February collection of peddler T.B. yielded the virus, while all other samples from this subject were negative for it. Samples from E.N. and J.B. likewise contained no virus. Peddler E.N. moved away in October; therefore, after September no further samples were obtained from this subject.

It is of interest to note that fruit peddler T.B. (a proved virus carrier) delivered fruits and vegetables to a household in which a 24 year old patient became ill with poliomyelitis and died in 1945. The fruit peddler was not tested for virus at that time. The route that this peddler, as well as several others, covered was the district of highest incidence of poliomyelitis in Salt Lake City in 1943, 1945 and 1946. Customers in this area bought fruits and vegetables from several peddlers; so it was impossible to determine whether any cases of the disease developing in this area were directly traceable to any single peddler.

Fruit Specimens.—Ten experiments were conducted using fruit washings as the test medium. From none of the samples tested was virus isolated (table 2).

COMMENT

From the results obtained, 1 fruit peddler of 3 tested over a long period harbored the virus of poliomyelitis in his stool. The virus was isolated once during the summer and once during the winter. This incidence suggests that the quantity of virus may vary in the stool from time to time. Like typhoid carriers, these persons who handle fresh fruits and vegetables may contaminate handled foodstuffs with sufficient virus to infect man but not monkeys. In ten experiments on washings from fruits, none of the samples yielded the virus of poliomyelitis when tested in monkeys. This series of experiments does not rule out the possibility of virus being present in sufficient quantities to infect man.

For a typhoid carrier under our supervision, each of five stools cultured over a period of seven months contained the organism. In six experiments, using samples of hand washings from this patient, no typhoid organisms were isolated for a period of six months. It may be that the poliomyelitis virus is likewise difficult to detect on foodstuffs handled by a virus carrier, but when such contaminated food is eaten the virus may multiply in the body of the human host.

SUMMARY

One of 3 fruit and vegetable peddlers tested over a period of eleven months harbored the virus of poliomyelitis in the stool twice during the test period.

In ten experiments in which washings from several kinds of fruits were used no virus of poliomyelitis was detected.

Dr. F. D. Gunn, of the Department of Pathology, University of Utah School of Medicine checked the histologic slides.

Department of Bacteriology, University of Utah School of Medicine.

MECHANISM OF HYPERBILIRUBINEMIA IN THE NEWBORN INFANT

Experimental Demonstration of Functional Hepatic Immaturity

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IT HAS been demonstrated that although only approximately 50 per cent of newborn infants become detectably jaundiced, cord blood and neonatal blood serum will, with rare exception, show hyperbilirubinemia when examined by chemical methods. After birth the serum bilirubin level rises for a few days, followed by a slow progressive fall to normal. In a series of 106 infants studied by Davidson and associates,[1] the median maximum serum bilirubin level was 5.7 mg. per hundred cubic centimeters, and only 2 infants from the group showed maximum levels of less than 1.0 mg. per hundred cubic centimeters. These workers demonstrated a high degree of correlation between the bilirubin level in the cord blood and the subsequent height and duration of hyperbilirubinemia in early postnatal life. They also showed a close association between the maximum level which the serum bilirubin attains and the duration of the hyperbilirubinemia. The fact that the red blood cell count and the packed red cell volume fall progressively during this period led many workers to assume that the hyperbilirubinemia is of a purely hemolytic type. If this factor were the only one involved, there should be some demonstrable relation between the amount of blood destruction and the degree of elevation of the serum bilirubin level. Salmon and Richman[2] were unable to demonstrate such a relation. The alternative explanation, that there exists some impairment of hepatic function during this period of life, was suggested by Ross and associates,[3] who observed that the average total excretion of bilirubin and urobilin in the stools during the neonatal period is lower in infants visibly jaundiced than in those not visibly so affected. However, direct attempts to assess neonatal

From the Departments of Pathology and Pediatrics, Southwestern Medical College of the Southwestern Medical Foundation.

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2. Salmon, G. W., and Richman, E. E.: Liver Function in Newborn Infant, J. Pediat. **23**:522-533 (Nov.) 1943.

3. Ross, S. G.; Waugh, T. R., and Malloy, H. T.: The Metabolism and Excretion of Bile Pigment in Icterus Neonatorum, J. Pediat. **11**:397-408 (Sept.) 1937.

hepatic function by means of the sulfobromophtalein excretion test,[4] the standard bilirubin excretion test[5] and the cephalin-cholesterol flocculation test[2] have failed to demonstrate impairment of hepatic function which can be correlated with the presence or absence of clinical icterus. During the past several years a number of authors have suggested that prenatal and neonatal blood destruction may be due to incompatibilities between maternal and fetal blood groups, and Halbrecht[6] recently stated that all forms of icterus in the newborn, physiologic as well as pathologic, are purely hemolytic in origin. The present investigation reports further studies germane to the entire problem.

METHODS AND MATERIAL

Twenty-one consecutive normal newborn infants, weighing between 3,200 and 3,400 Gm., were followed from the day of birth until their discharge from the hospital nursery on the sixth or seventh day of life by means of daily red blood cell counts and determinations of hemoglobin concentration, red cell volumes and plasma bilirubin levels. In all instances save 1, the bilirubin content of the meconium excreted during the first three days was determined. For a similar series of 50 normal infants a daily estimation of plasma bilirubin was made; the infant's and the mother's blood type and Rh type were determined in each instance, and a search was made for antibodies to A, B and Rh antigens.

The velocity constant of excretion of bilirubin was determined by the technic of Weech, Vann and Grillo[7] for 11 infants from 1 to 10 days of age exhibiting hyperbilirubinemia and for 7 infants from 9 to 20 days of age with normal plasma bilirubin levels.

The blood counts, red cell volume estimations and blood typing were done by standard methods. National Bureau of Standards pipets were used. Serum bilirubin levels were determined by the microprocedure of Malloy and Evelyn[8] and also by the technic of Weech and associates.[7] Bilirubin in the stool was determined according to the method of Evelyn and Malloy[9] and urobilinogen by the photo-

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6. Halbrecht, I.: Role of Hemoagglutinins Anti-A and Anti-B in Pathogenesis of Jaundice of Newborn (Icterus Neonatorum Precox), Am. J. Dis. Child. **68**:248-249 (Oct.) 1944.

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electric method of Schwartz, Sborov and Watson.[10] All determinations were carried out in duplicate.

RESULTS

Figures 1 and 2 show the relation existing between the maximum plasma bilirubin level and the maximum drop in red cell count and in

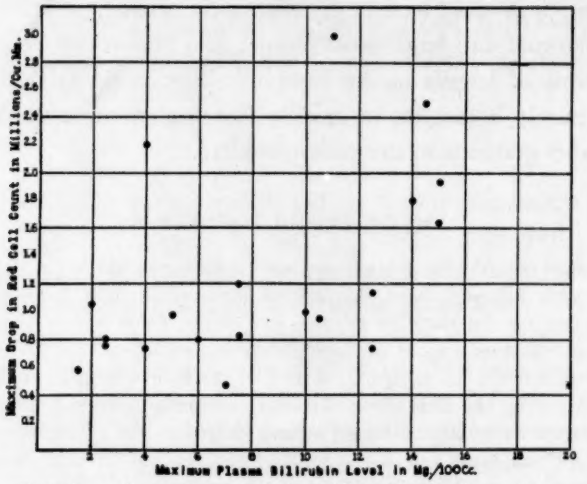

Chart 1.—Relation of maximum plasma bilirubin level to the maximum drop in red cell count of 21 infants during the first week of life.

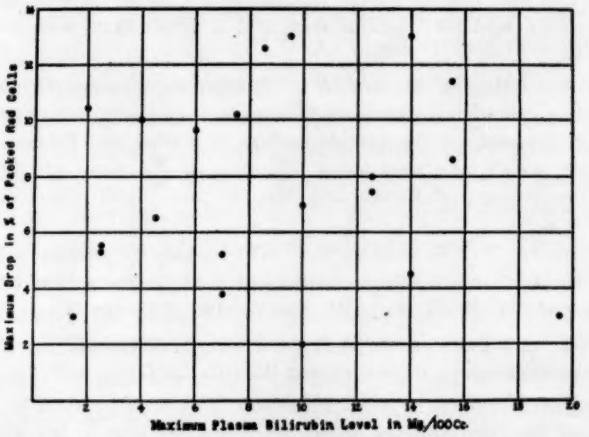

Chart 2.—Relation of maximum plasma bilirubin level to maximum drop in packed red cell volume of 21 infants during the first week of life.

packed red cell volume, respectively, of 21 infants during the first week of life. At first glance, there appears to be a trend toward greater degrees of hyperbilirubinemia in those subjects whose red cell count drop-

10. Schwartz, S.; Sborov, V., and Watson, C. J.: Studies of Urobilinogen: Quantitative Determination of Urobilinogen by Means of Evelyn Photoelectric Colorimeter, Am. J. Clin. Path. **14**:598-604 (Dec.) 1944.

ped the most, but statistical analysis of the data reveals that the average drop in red cell count in the group attaining a bilirubin level of less than 8 mg. per hundred cubic centimeters is 930,000 ± 470,000, as compared with an average of 1,520,000 ± 720,000 for the group whose

TABLE 1.—*Relation of Bilirubin Content of First Meconium to Maximum Plasma Bilirubin Attained During the First Week of Life*

Maximum Plasma Bilirubin Level, Mg./100 Cc.	Bilirubin Content of First Meconium, Mg./100 Gm.	
	Individual Infants	Average
Under 5	25.2; 36.0; 44.0; 59.6; 84.4; 102.0	58.5
5 to 10	16.0; 24.0; 24.2; 30.2; 45.8; 62.2	33.7
Over 10	12.2; 16.2; 19.8; 22.0; 32.8; 34.0; 34.2; 37.0	26.0

TABLE 2.—*Relation of the Velocity Constant of Excretion of Bilirubin (K) to the Degree of Bilirubinemia*

Patient	Age, Days	Bilirubin Level, Mg./100 Cc.	K/Mg. Min./Mg.^{2}
D.	1	2.5	1.96×10^{-3}
R.	7	2.6	1.20×10^{-3}
B.	10	3.8	0.43×10^{-3}
Bra.	1	4.3	0.65×10^{-3}
E.	1	5.4	0.56×10^{-3}
Jo.	2	5.5	1.60×10^{-3}
V.	1	6.3	0.56×10^{-3}
Li.	2	6.3	1.23×10^{-3}
Bu.	2	7.8	0.31×10^{-3}
Ju.	5	8.9	0.96×10^{-3}
We.	3	17.4	0.36×10^{-3}
Wo.	6	0.45	4.5×10^{-3}
Jo.	6	0.45	4.5×10^{-3}
La.	20	0.50	4.0×10^{-3}
Cl.	18	0.54	3.5×10^{-3}
D.	8	0.60	4.0×10^{-3}
E.	9	0.80	3.0×10^{-3}
Li.	6	0.90	2.8×10^{-3}

Values above 2.5×10^{-3} mg. units indicate hepatic function; values between 2.0 and 2.5×10^{-3} mg. units, presumptive evidence of diminished excretory function; values below 2.0×10^{-3} mg. units, positive evidence of impaired function.

bilirubin levels exceed 8 mg. per hundred cubic centimeters. This difference is not statistically significant. No correlation is apparent between drop in packed red cell volume and degree of hyperbilirubinemia.

Table 1 shows the relation of the bilirubin content of the first meconium to the maximum plasma bilirubin level attained during the first week of life. Although the three groups display considerable overlapping, the average excretion of bilirubin in the meconium is more than twice as great for the group of infants whose maximum plasma bilirubin levels were under 5 mg. per hundred cubic centimeters as for the group whose maximum plasma bilirubin levels exceeded 10 mg. The data thus far presented were obtained for infants of approximately the same weight, since it is known that the magnitude of blood pigment metabolism, particularly the amount of bile pigment excreted, is a function of the total red cell mass and will thus be related to the weight of the subject.

Table 2 shows the results obtained with the test of Weech, Vann and Grillo for rate of bilirubin excretion, which is independent of the initial bilirubin level of the plasma. The velocity constant of excretion of bili-

TABLE 3.—*Relation of Maternal and Fetal Isohemagglutinins to the Development of Neonatal Hyperbilirubinemia*

	Average Plasma Bilirubin, Mg./100 Cc.			
	Cord Blood	1st Day	2nd Day	3rd Day
40 infants in whom isoimmunization by A, B or Rh factors was not possible	2.0	4.5	6.0	7.0
10 infants in whom isoimmunization by A, B or Rh factors was possible	2.6	4.6	6.9	7.8

rubin for those infants whose plasma bilirubin levels were elevated differs greatly from the constant for the group in which the plasma bilirubin had returned to normal. It will be seen that in every instance of hyperbilirubinemia the velocity constant has a value below 2.0×10^{-3} mg. units, which Weech and associates considered positive evidence of impaired hepatic function. In every instance in which the plasma bilirubin level was normal, the velocity constant was also normal. In only 4 instances was it possible to obtain the value of the velocity constant of excretion of bilirubin for an infant during the period of hyperbilirubinemia and again after the hyperbilirubinemia had subsided. These patients were E., Jo., D. and Li., and it will be seen that the velocity constants of excretion of bilirubin were decidedly decreased during the hyperbilirubinemic phase and attained normal levels when the plasma bilirubin returned to normal.

Table 3 shows the relation of maternal and fetal isohemoagglutinins to the development of neonatal hyperbilirubinemia. On the basis of the

blood type of mother and infant, the infants were divided into two groups: those in whom isoimmunization by A, B or Rh factors was possible and those in whom such isoimmunization was not possible. It will be seen that the two groups do not differ significantly in the level of plasma bilirubin, either in cord blood or in samples of blood taken on the first, second or third day of postnatal life.

COMMENT

The lack of correlation between the magnitude of the drop in red cell count and packed red cell volume and the height to which the plasma bilirubin level rises during the first week of postnatal life confirms Salmon and Richman's report in this respect and extends their observations, since the determinations of the present data were based on the degree of hyperbilirubinemia rather than on the presence of clinical icterus. If variation in the rate of excretion of bile pigment into the bowel before birth affects the level of bilirubin in the fetal plasma, one would expect an inverse relation between the concentration of bile pigment in the first meconium and the bilirubin concentration both in the cord plasma and in the infant's plasma during the first few days of life. The data of Ross and associates[3] suggested that such a relation may exist, the meconium of the first day averaging 48.2 mg. of bile pigment per hundred cubic centimeters for 21 infants without jaundice and 34.8 mg. per hundred cubic centimeters for 14 infants with jaundice. These differences are not striking, but, since size of infant was not taken into consideration and the groups were divided on the basis of clinical icterus rather than on the degree of hyperbilirubinemia, they may be significant. In the present study the infants were divided into three groups on the basis of the degree of hyperbilirubinemia which developed during the first week of life; and, although considerable individual variation existed in each group, the inverse correlation of the bilirubin content of first meconium to subsequent height of plasma bilirubin is sufficiently impressive to suggest that functional immaturity of the liver operating before birth has an effect on the concentration of bilirubin in the cord blood and in the plasma during the early postnatal period.

Lin and Eastman,[5] using the conventional bilirubin clearance test were unable to demonstrate differences in hepatic function between icteric and nonicteric infants. These investigators utilized percentage retention of injected bilirubin after four hours as a measure of hepatic function and assumed that the rate of excretion of bilirubin is not influenced by the basal level of bilirubin in the plasma. Weech and associates showed that this assumption was incorrect because the rate of excretion determined experimentally appears to be approximately proportional at any moment to the square of the concentration of bilirubin in

the plasma. Since almost all infants have elevated plasma bilirubin levels, it is necessary to employ a test which is independent of the initial bilirubin concentration of the plasma. The method of Weech and associates for measuring the excretory capacity of the liver fulfils this criterion and enables one to calculate a velocity constant of excretion of bilirubin which defines the efficiency of the liver independent of the initial bilirubin concentration of the plasma. With the use of this test it will be seen that the bilirubin excretory capacity of those infants who show bilirubin retention at the time of the test is definitely impaired, and that no impairment exists in infants of comparable age who have normal plasma bilirubin levels.

Since the plasma bilirubin pattern of either cord plasma or plasma obtained during the first three days of postnatal life in the group of infants for whom isoimmunization to A, B or Rh factors was not possible does not differ significantly from that in the group for which such isoimmunization was theoretically possible, it is fairly certain that isoimmunization and subsequent blood destruction are not concerned in the development of physiologic icterus.

SUMMARY AND CONCLUSION

There is no demonstrable relation between the magnitude of the drop in red blood cell count and packed red cell volume and the degree of hyperbilirubinemia which develops in early postnatal life. In a series of infants in whom the blood volumes may be assumed to be comparable on the basis of weight, the amount of bile pigment in the first meconium and the height to which plasma bilirubin rises during the first weeks of postnatal life show an inverse correlation, suggesting functional immaturity of the liver operating before birth as a cause for elevated serum bilirubin levels in the cord blood. Direct assessment of hepatic function from determination of the velocity constant of excretion of bilirubin by a method which is independent of the initial level of bilirubin in the plasma shows pronounced impairment of hepatic function in infants exhibiting hyperbilirubinemia and normal excretory function in a comparable group without hyperbilirubinemia. The plasma bilirubin pattern for three days after birth in a group of infants compatible with their mothers with respect to A, B and Rh factors does not differ from that of a comparable group incompatible with their mothers with respect to these factors. Isoimmunization, therefore, does not appear to play a part in the production of physiologic hyperbilirubinemia in the newborn. The evidence points to functional immaturity of the liver operating before birth and for a variable period after birth as the cause of bilirubin retention in the neonatal period.

2211 Oak Lawn Avenue.

Case Reports

UNILATERAL MULTICYSTIC KIDNEY IN INFANCY

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WITH THE modern trend toward specialization, more and more newborn infants are receiving thorough examinations by pediatricians. This is responsible for the early discovery of conditions which heretofore presented themselves only in late stages during childhood or adult life. The promptness with which infants are now subjected to specialized examinations and given definitive treatment has decreased materially the mortality and morbidity of many diseases.

It is our purpose to present 2 recent cases of unilateral multicystic kidney and to emphasize the major points in diagnosis and management of the condition.

ETIOLOGIC AND PATHOLOGIC ASPECTS

There has been much speculation in the last decades concerning the cause of multicystic kidney.[1] Workers have not agreed on its etiologic basis; for this reason we omit a discussion of such theories. It is, however, fairly well established that the condition is pathologically unlike polycystic kidney.

Multicystic kidney is usually bilateral and results in death of the fetus in utero.[2] The disease represents a not infrequent cause of stillbirth. Rarely, the disease is unilateral, and it is with cases of this type the present paper is concerned.

A multicystic kidney is usually several times enlarged, and grossly it consists of many cysts filled with a straw-colored fluid of high urea content. The cysts vary from a few millimeters to several centimeters in diameter. They are held together by loose connective tissue and almost completely replace the normal renal tissue. Many of the larger cysts are connected with the renal pelvis by a small orifice, which permits the passage of the cystic fluid into the renal pelvis when external pressure is applied to the cysts.

From the Department of Urology, Emory University School of Medicine and Grady Memorial Hospital.

1. Kampmeier, O. E.: A Hitherto Unrecognized Mode of Origin of Congenital Renal Cysts, Surg., Gynec. & Obst. 36:208-216, 1923.

2. Bugbee, H. G., and Wollstein, M.: Surgical Pathology of the Urinary Tract in Infants, J.A.M.A. 83:1887-1898 (Dec. 13) 1924.

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Microscopically, the cysts are lined with a single layer of epithelial cells. The remainder of the wall is made up entirely of fibrous tissue. Near the center of the whole cystic mass there is usually a small, solid area of renal tissue.

In many of the reported cases absence of the ureter was noted, and it is of interest that in both our cases ureteral obstruction was complete. In 1 case the entire ureter was absent, while in the other it showed no lumen microscopically in the upper third. It is possible that the etiologic basis of the disease is congenital ureteral obstruction and that the so-called cysts represent simply dilated and anomalous major and minor calyxes.

The dissimilarity of multicystic and polycystic disease of the kidney is great, and the disease may be differentiated on gross examination.[3] In polycystic disease, the kidney maintains its usual configuration but is riddled with cysts which are in general of approximately the same size. The cysts are dispersed throughout the kidney with islands of normal renal substance separating them. In multicystic renal disease the organ appears as a cluster of cysts which vary considerably in size. The usual configuration of the kidney is not maintained. The communication of some cysts with the renal pelvis by a small orifice in the cyst wall indicates that the disease may result from obstruction at a more distal portion of the renal excretory system than in polycystic disease, which is known to be caused by obstruction in the proximal portion of the tubular system.

DIAGNOSTIC FEATURES

Cystic renal disease in general may conveniently be classified clinically into medical or surgical types on the basis of the predominating symptoms.[4] The medical type, manifested by renal insufficiency, anemia, hypertension and various general symptoms, is seen only in bilateral disease, usually classic polycystic kidney, and we are not concerned with it.

In unilateral disease in which the other kidney compensates for the cystic one, these general symptoms do not appear.[5] The condition under discussion thereby falls into the surgical classification, with symptoms referable only to the kidney.

The cardinal sign is a mass in the region of the kidney. This may be large and easily detected, or the enlargement may be only slight, requiring careful palpation. When the mass is nodular and irregular, an important clue to the diagnosis is present, but nodulation may be masked by muscular resistance. The infant may appear surprisingly healthy in general.

Hematuria may occasionally occur to direct attention to the urinary tract, but it is oftener absent.

Once the pediatrician has suspected an abnormality of the kidney, the diagnosis is clinched by urologic examination. It should be stressed

3. Schwartz, J.: An Unusual Multicystic Kidney in an Infant, J. Urol. **35**:259-263, 1936. Lynch, K. D., and Thompson, R. F.: Unilateral Multicystic Kidney in an Infant, ibid. **38**:58-60, 1937.

4. Bell, E. T.: Cystic Disease of the Kidneys, Am. J. Path. **11**:373-419, 1935.

5. Wakely, C. P. G.: A Case of Unilateral Polycystic Kidney in a Child One Year, Eight Months, Brit. J. Surg. **18**:162-165, 1930.

that all the diagnostic methods of urology are applicable to infants. No longer should tender age and size preclude even a newborn child from complete investigation of the urinary tract by modern methods.

Excretory urography is easily accomplished by the subcutaneous route if the intravenous injection is not feasible. In unilateral multicystic disease, such examination shows a functionless kidney with a normal opposite kidney.

Cystoscopy with retrograde pyelography is no longer a formidable procedure with the improved instruments now available. Anesthesia, if needed, is easily induced with a "sugar teat" of whisky or by the open drop ether method, and this procedure is indicated for final diagnosis and decision as to management. If there is hematuria, cystoscopy establishes the source of it. If an excretory urogram has revealed a functionless kidney, cystosopic examination may show anomaly, atresia or blockage of the ureter on the side involved.

MANAGEMENT

After establishment of the fact of a functionless kidney, with a mass in the renal region and a normal opposite kidney, surgical exploration of the kidney is indicated. This view is not radical, for only by this method can it be proved whether or not there is a neoplasm. In the event of the latter nephrectomy is the sole method of treatment that offers a cure. If the mass proves to be a kidney destroyed by multicystic disease, nephrectomy is likewise indicated. The procedure is usually easy, for in this disease no dense inflammatory adhesions are present and the blood supply is small in comparison with that of a normal kidney.

Since infants tolerate surgical treatment well, it again should be emphasized that age and size are no barrier to proper surgical procedures. The preoperative nutritional state of the infant is managed without regard to surgical intervention, which offers no complication. The child may be fed intravenously for twenty-four to forty-eight hours, if indicated, but it is usually unnecessary.

After recovery, examinations to determine the state of the remaining kidney should be repeated at regular intervals.

REPORT OF CASES

Case 1.—F. W., a premature Negro girl weighing 2,000 Gm., was born of a mother who had hypertensive heart disease and died in shock shortly after delivery. A routine physical examination was made by a pediatrician, with discovery of a mass in the left upper quadrant of the abdomen. The mass was described as fixed and nodular, extending from beneath the costal margin to the iliac crest. Urinalysis at this time revealed a few red blood cells per high power field in an uncentrifuged specimen.

An excretory urogram was made a few days later, after the infant had been properly dehydrated. The examination showed that the upper portion of the right urinary tract was normal with failure of the left kidney to excrete the dye. A mass was observed on the urograms in the region of the left kidney, which was approximately the size described previously.

Since the findings on excretory urograms strongly indicated a pathologic condition of the left kidney, a cystoscopic examination was done, using a no. 12-F

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infant cystoscope. The bladder was normal, and clear urine was seen to spurt from the right ureteral orifice. The left ureteral orifice could not be visualized.

During the following week the mass almost doubled in size, and surgical exploration of the right kidney was considered indicated, with a congenital anomaly of the left kidney as the most likely diagnosis. The possibility of renal neoplasm was also considered.

When the child was 14 days old, exploration of the left kidney was done, with the child under local anesthesia induced with 1 per cent procaine hydro-

Typical multicystic kidney, with many cysts of various sizes, causing loss of normal configuration.

chloride U.S.P., supplemented with a "sugar teat" of whisky. A typical multicystic kidney was observed and removed. The patient withstood the procedure well and received 100 cc. of whole blood intravenously during the operation.

Pathologic Observations.—A report of the pathologic examination is quoted in detail:

"Gross Examination: The specimen consisted of a pinkish gray, multicystic mass of tissue, weighing 37 Gm. and measuring 6 by 4 by 3 cm. The cysts varied from less than 1 mm. to more than 2.5 cm. in diameter. Thirteen cysts larger than 1 cm. were counted. One surface had a depression which represented the hilus of the kidney. The pelvis was slightly dilated but came abruptly to a rounded end

at the usual ureteropelvic juncture, and the ureter was continued as a thin filament insufficiently patent to allow the fluid to flow from the pelvis. The pelvis divided into two major calyxes and each of these into at least three minor calyxes. As the pelvis was opened, approximately 15 cc. of clear, straw-colored fluid escaped and about half the cysts collapsed. No normal renal tissue was seen on cut surface, the entire structure being composed of gray-walled cysts and calyxes.

Microscopic Examination: The sections showed numerous large and small cystic spaces and a small amount of renal parenchyma. The cystic spaces were lined with cuboidal or flattened epithelium, depending on how distended the cyst was. The renal parenchyma showed tubules and glomeruli, some of which simply projected slightly into a much dilated glomerular space. The tubules consisted of both secretory and collecting types. Some of the collecting tubules were dilated. A section through the pelvis and ureter showed thin surface epithelium of flattened cells one or two layers deep in the pelvis and no lumen in the ureter, which was composed of fibrous tissue. A small fragment of cartilage was seen in one section.

Postoperative Course.—After the operation, the patient took her formula well and began at once to gain weight. She was discharged on the thirteenth postoperative day in good general condition, weighing 2,600 Gm. At the end of one year the child weighed 9,979 Gm. and appeared to be healthy in every respect.

CASE 2.—B. S., a 2 month old Negro girl, weighing 11 pounds 6 ounces (5,160 Gm.), was admitted to the urologic service for study of a smooth, firm mass in the right renal region. This was discovered in routine well baby examination. The mass was movable and about the size of a golf ball. The child appeared healthy in all other respects. The urine was normal.

An excretory urogram demonstrated a normal left kidney and ureter, but no dye was excreted on the right side. Cystoscopic examination revealed the bladder to be normal; however, attempts to make a right retrograde pyelogram failed, owing to obstruction in the ureter 2 cm. from the bladder. The catheter could not be passed up the ureter, nor could contrast medium be injected past the obstruction. A second, separate attempt to demonstrate the right kidney met the same low obstruction in the ureter.

On the basis of a functionless kidney on the right side, with a mass in the renal region, while the opposite kidney was normal, a diagnosis of hydronephrosis or multicystic kidney was made, with the possibility of neoplasm to be excluded.

Surgical exploration of the affected kidney was made, with the patient under anesthesia induced by the open ether method. A multicystic kidney was observed, and nephrectomy was performed. The patient made an uneventful recovery and was discharged on the fourteenth day. She has been followed for twelve months and appears entirely healthy, with the remaining kidney normal.

The pathologic report on the specimen in this case so closely resembles that of the first that it is unnecessary to present it in detail.

SUMMARY

Etiologic and pathologic aspects of unilateral multicystic kidney are discussed. Diagnosis is based on complete urologic examination, which is applicable to even the smallest infant. Management of the condition is surgical, and it is stressed that age and size are no barrier to proper surgical treatment.

Two cases are reported in which treatment by nephrectomy was successful.

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PSEUDOHERMAPHRODITISM IN TWINS

Report of the Tenth Case

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THIS REPORT of pseudohermaphroditism in twins is the tenth such case to appear in the literature. The twins, living, as of the time of writing, were born March 13, 1947, and are classified as pseudohermaphrodites of the female external type.

Brewster and Cannon[1] classified pseudohermaphrodites as follows: (1) the male type, in which the external characteristics of the male predominate, the person thus assuming the role of a male, and (2) the female type, in which the external characteristics of the female predominate, the person thus assuming the role of a female.

The majority of cases recorded are of a pseudo type, in which the formation of the external genitalia is such as to give rise to the impression that both male and female organs are present, but in which, at operation or necropsy the glands of one sex are observed. The other sexual parts are mixed or are intermediate and of various degrees of development. It is often observed that only at adolescence does the real sex of that person become manifest. Among pseudohermaphrodites the male type predominates.

REPORT OF A CASE

The mother of the twins,[2] E. H., aged 19, was white, American and a primipara.

The last menstrual period had occurred about Aug. 27, 1946. The expected date of confinement was June 3, 1947. The babies were born on March 13. The mother was a circus attendant and had made only one prenatal visit to a physician in another city. She arrived at the hospital at 3:30 a.m.; the first baby was born at 3:45 a.m. and the second eighteen minutes later. The membranes were ruptured before her arrival at the hospital. She had one placenta, but two cords.

A satisfactory history was difficult to secure. The mother stated that there was no history of twins in either her family or her husband's family and no occurrence of physical or mental defectiveness, except that her husband's brother had some disease in infancy which left him with a mind of a 6 year old child; he was 16 at the time of writing. She and her husband had separated, and little more is known. She denied that there was any consanguinity. She also denied that either of

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Dr. W. C. Thomas aided in the photography and in the examination and measurements of the patients.

1. Brewster, H. F., and Cannon, H. E.: Hermaphroditism, New Orleans M. & S. J. **82**:76 (Aug.) 1929.

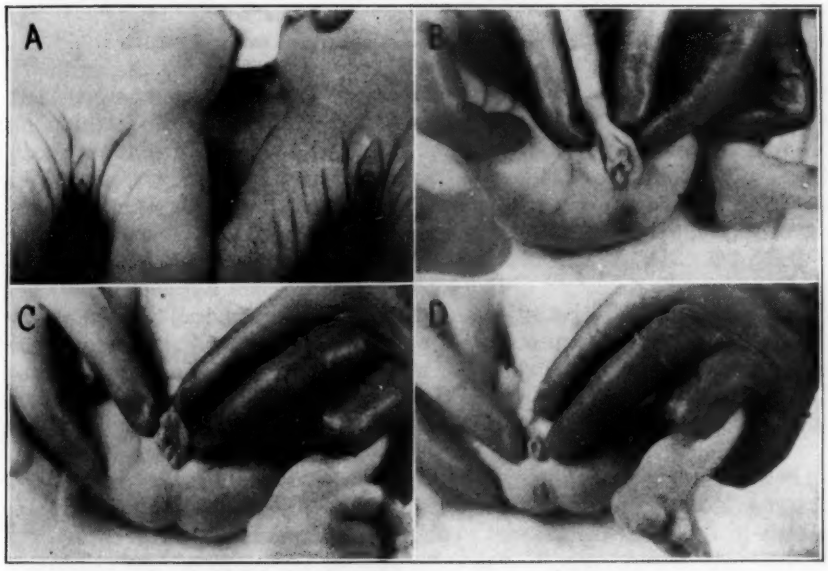
2. The mother was admitted to the maternity service of Dr. Hqward Coe, City Hospital, Brunswick, Ga.

the two families was related to the so-called true hermaphrodite in the circus. The mother sold tickets to the side show for this hermaphrodite.

As indicated, the babies were identical at birth, each weighing 3 pounds 8 ounces (1,587.56 Gm.). They were born apparently about six to seven weeks prematurely. They cried promptly, and physical examination showed no abnormalities except as described in this paper.

Both little girls showed identical characteristics, with less than 1 or 2 mm. difference in measurements. The measurements recorded here were made when the children were 52 days of age and weighed 6 pounds 2 ounces (2,778.24 Gm.) and 6 pounds 7 ounces (2,819.99 Gm.), respectively. Because of their similarity, the description from this point on will be of one child only.

The dorsum of the elongated clitoris (*A* of the figure) was 23 mm. from the tip to the symphysis pubis. The thickness of the structure was 10 mm. The dorsum



Photographs of the twins, showing the aberrations.

of the clitoris was covered by skin for about three quarters of the circumference. This skin was continuous with the skin of the symphysis. On each side and below, this skin fused with the mucous membrane of the labia minora, which were covered by mucous membrane throughout.

From this anterior organ the labia minora circled the vagina and fused posterior to the vagina. The labia majora were present and normal in structure, though about 60 per cent of normal size. There was a third lip evident, which merely circled the vagina as a cuff. This was mucous membrane and seemed to be an outpouching of the vaginal mucosa, forming a cuff of 3 to 5 mm. high (*C* and *D* of the figure). The vaginal canal was demonstrated with difficulty. At first I thought that it was not present and that the cuff merely surrounded an area of dimpled and folded skin. However, by using a 4 mm. otoscope, a small opening in these folds was followed and a tiny vagina entered. The vaginal canal was followed for about ½ inch (about 1.3 cm.), and a cervix was brought into view. The vagina was not as large as in infants of corresponding weight.

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The enlarged clitoris was covered by mucous membrane on the under side, and a definite corpora cavernosa, about three quarters of the width of the clitoris, was palpated throughout. No glands was palpated. Viewed anteriorly (*B* of the figure) the impression was gained that a mere fusion along the lower fourth of this structure would produce a penile structure. Figure *C* shows that a groove was at the extremity of the clitoris and the external urethra at the base of the structure, but the urethra formed an external canal for another 2 to 3 mm. before turning inward. Had this urethra remained covered throughout and made its exit in this groove, it would have constituted a male urethra.

Roentgenograms of the wrists of both of these infants showed no development of carpal bones; therefore, the bone age was not ahead of the chronologic age (as seen in the adrenocortical syndrome).

From this examination the infants were classed as monozygotic female pseudohermaphrodites of the external type.

COMMENT AND REVIEW

The word hermaphrodite is derived from Greek mythology. Hermaphroditus was the son of Hermes and Aphrodite. While bathing he became joined in one body with Salmacis, the nymph of a fountain in Caria. This fountain was fabled to effeminate all who drank of it.[3]

In true hermaphroditism the functional gonads of both sexes are present. In pseudohermaphroditism there is an internal and/or external confusion in the sex organs. McCullaugh[4] expressed the belief that, in general, the immediate factor in determination of sex is the gene but that the degree of sexual differentiation is determined by hormonal influences. By such a conception the occurrence of strong or weak male and female forms may be explained by an imbalance of male or female sex hormones. The hormones have an effect on the degree of development of structure from a foundation laid by genetic factors.

This endocrine imbalance may be either in the mother or in the embryo, though probably in the mother, as such anomalies have been observed in the same family.[5] A tumor of the cortex of the adrenal glands in the fetus may lead to congenital pseudohermaphroditism—the adrenocortical syndrome.[6] The only sign or symptom of this syndrome which might be expected in the neonatal period would be an acceleration of maturation of the skeleton. I did not observe the bone age to exceed the chronologic age in these infants.

Determination of relative male and female development is desirable as early as possible. Several cases were found in the literature in which the parents of an infant were told at birth merely that there was an ab-

3. Webster, N.: New International Dictionary, ed. 2, Springfield, Mass., G. & C. Merriam Company, 1941.

4. McCullaugh, E. P.: Male Gonads, in Tice, F.: Tice's Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1927, vol. 8, chap. 5, p. 343.

5. Stirling, W. C.: Report of a Case of True Hermaphroditism, J. Urol. **56**:720 (Dec.) 1946. Davis, W.: Pseudo-Hermaphroditism Occurring in Two Children of One Family, M. J. Australia **1**:860 (June 11) 1927.

6. Rowntree, L. G., in Cecil, R. L.: Textbook of Medicine, ed. 6, Philadelphia, W. B. Saunders Company, 1943, p. 1236. Wintersteiner, O.: The Adrenogenital Syndrome, J.A.M.A. **116**:2679 (June 14) 1941.

normality of sex. Moehlig and Allen[7] reported such a case, in which the patient at birth seemed to be a girl; later male characteristics developed. A similar case was reported in *The Journal of the American Medical Association.*[8] Young[9] reported many cases of sexual confusion. In 7 of the patients sexual characteristics opposite those displayed in childhood developed during adult life. Some of the patients continued to lead the life of one sex even after it was demonstrated that their gonads were more typical of the opposite sex.

Rubovits and Saphir[10] reported a case of a male pseudohermaphrodite who had lived an abnormal female existence for thirty-nine years. Even after it was determined that male characteristics predominated it was considered best to let this person continue to live as a woman. The decision was based on the patient's wishes and social adjustments. Therefore, the rudimentary vagina was enlarged and the small penis and testicles were removed.

To avoid such years of confusion in pseudohermaphrodites, operation, or other procedures to determine sex, is desirable as early as possible.[11] Before school age the anatomic development is far enough along to permit a diagnosis and to facilitate plastic surgical treatment. Certainly, prepubertal classification, and plastic work if indicated, will give a much better chance for final sex development.

A recent study of hermaphrodites by Ellis[12] has thrown more light on the importance of psychogenic and environmental factors in homosexuality. He observed that the hermaphrodite assumes the sexual role that is in accordance primarily not with his or her internal or external somatic characteristics but rather with his or her feminine or masculine upbringing. Therefore, heterosexuality in hermaphrodites, as in nonhermaphrodites, is primarily influenced by environmental and not by endocrine or other physiologic factors, as in the patients previously referred to,[13] who preferred to maintain the sex to which they had been accustomed, even when they were proved to be of the opposite sex.

As to the excreted pregnandiol in youthful female pseudohermaphrodites, Genitis and Bronstein[14] studied a boy and a girl aged 10 and 4, respectively. They pointed out that the extraction of large amounts of

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7. Moehlig, R. C., and Allen, N. M.: Intersexuality, J.A.M.A. **112**:1938 (May 13) 1939.

8. Sex Intergrade, Queries and Minor Notes, J.A.M.A. **131**:494 (June 1) 1946.

9. Young, H.: Some Hermaphrodites I Have Met, New England J. Med. **209**:370 (Aug. 24) 1933.

10. Rubovits, W. H., and Saphir, W.: Intersexuality, J.A.M.A. **110**:1823 (May 28) 1938.

11. Pseudohermaphroditism, Queries and Minor Notes, J.A.M.A. **111**:2415 (Dec. 24) 1938.

12. Ellis, A.: The Sexual Psychology of Human Hermaphrodites, Psychosom. Med. **7**:108 (March) 1945.

13. Young.[9] Rubovits and Saphir.[10]

14. Genitis, V. E., and Bronstein, I. P.: Pregnandiol Excretion in Female Pseudohermaphroditism (Congenital Adrenal Hyperplasia): Studies in Two Cases, J. A. M. A. **119**:704 (June 27) 1942.

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urine in children is necessary and that sometimes a collection of a forty-eight hour specimen produces a precipitate of no significance. Evidently such a procedure would offer no information in these cases, even if a forty-eight hour, or longer, specimen could be obtained from an infant. Also, there is no standard for comparison in infants. Genitis and Bronstein made determinations in other children and concluded that their patients, who were of the adrenogenital type, did show an elevated titer for pregnandiol excretion. Stover and Pratt,[15] however, observed no pregnandiol in the urine of a 3 year old child with the adrenogenital syndrome.

As to the actual cases of pseudohermaphroditism in twins, Rhodes,[16] in 1943, reported the ninth case to appear in the literature. His patients were pseudohermaphrodites of the male external type, and the report was made while the children were living. No previous cases were found other than those reviewed by Rhodes, and since 1943 no report of the incidence of this condition in twins has been found in the literature. He described the 8 previous cases and included a bibliography. The reports were from 1573 to 1921. Of these patients described, 6 sets of twins either were born dead or died in early infancy and the seventh showed only a mild type of genital abnormality, glandular hypospadius; the eighth set was first discovered at 17 years of age.

SUMMARY

The case of pseudohermaphroditism in twins described herein is the tenth such case to appear in the literature. The twins were living as of the time of writing, and the classification and study were based on anatomic observation. It is not possible to go beyond an anatomic study in infancy, but early diagnosis and plastic work is desirable. Surgical treatment should be done at preschool age or, certainly, in the prepubertal period. Observation of the structural development and pregnandiol excretion may be supplemented by urethroscopic examinations, pneumoperitoneum and, if indicated, laparotomy, to determine the degree of sexual aberration present.

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15. Stover, R. F., and Pratt, J. C.: Progesterone Studies: Pregnandiol Excretion, Endocrinology **24**:29 (Jan.) 1939.

16. Rhodes, A.: Pseudohermaphroditism in Twins: Report of Case, Arch. Pediat. **60**:529 (Oct.) 1943.

Book Reviews

The Pathology of Nutritional Disease: Physiological and Morphological Changes Which Result from Deficiencies of the Essential Elements, Amino Acids, Vitamins and Fatty Acids. By Richard H. Follis Jr., M.D., Associate Professor of Pathology, Duke University School of Medicine, Durham, N.C. Price, $6.75. Pp. 291, with 110 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1948.

Follis attempts to characterize the morphologic and physiologic changes incident on deficiency in the diet elements of compounds. In any survey of the field of nutritional deficiency, one is easily confused by the multitude of pathologic changes which have been ascribed to any specific deficit. Therefore, Follis has performed a welcome service in summarizing authoritatively the currently accepted descriptions of nutritional deficiency.

The book is a small one and devotes itself to single deficiencies as seen in mammals. The emphasis throughout is on morphologic changes. The author states that his physiologic data are intended merely as a brief survey and introduction to the subject. Follis organizes his subject into six parts. Four of these are devoted to the deficiencies respectively of the elements, amino acids, fatty acids and vitamins. The bulk of the material is concentrated in the chapter on vitamins. The remaining two chapters, while less encyclopedic, are notable contributions that members of the medical profession may read with profit. They provide a point of vantage from which may be integrated the entire field of pathology and physiology in relation to specific nutritional chemical compounds. One of these chapters is entitled "Dietary Deficiencies in General" and the other "The Pathologic Anatomy of Specific Tissues." They are cross indexes of the changes in regard to the general mode of action in deficiency and the issues affected.

If any criticism is to be leveled at this volume, it is in the nature of regret that more of the useful available material is not included. In part, the judiciously winnowed bibliography meets this criticism, but one would have welcomed, for example, a description of the pathologic pictures caused by excesses of the single elements, as well as by their deficiency.

The author is to be commended for his attitude in correlating the large mass of experimental data with clinical and human pathologic material. He shows conservatism and wisdom in declining to emphasize the possible etiologic relationships between human morphologic change seen at autopsy and that resulting from experimental deficiencies. It is obvious that the author has had a wide acquaintance with both types of material. He points out in detail in which fields future work should be done in the study of multiple deficiencies.

A final word of praise may be bestowed on the clarity of Dr. Follis' presentation and on his abstinence from speculative discussion. While admittedly his opinions cannot be free from subjective bias, his statements on the whole are generally accepted, and controversial subjects are treated with fairness.

Particularly for the young investigator who is beginning his acquaintance with the field of nutrition is the book valuable. Herein are contained many suggestions for problems which deserve investigation. It is surprising that the lacunas

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in present knowledge are so numerous and extensive; the physiologist, nutritionist and pathologist may well survey the spotty state of knowledge as exemplified in this book and acquaint themselves with the materials and methods as well as the basis of present theory.

A Handbook on Diseases of Children. Fifth edition. By N. Bruce Williamson, M.D., Price, $4.50. Pp. 408, with 86 illustrations. Baltimore: The Williams & Wilkins Company, 1947.

The text has been thoroughly revised and includes many of the advancements made in the field of pediatrics since the fourth edition was published two years ago. Each chapter contains added material. The author has emphasized the new therapeutic methods, with special attention to penicillin.

The book retains the physical makeup and features of the previous edition. Little attention is given to differential diagnosis.

This text may be recommended as a reference handbook.

Nutrition in Relation to Cancer. By C. G. King and others. Price, $2. Pp. 140, with 51 tables and 23 illustrations. Annals of the New York Academy of Sciences, Volume 46, Article 1. New York: The New York Academy of Sciences, 1947.

One of the many interesting problems concerning cancer is that of cell growth and the hereditary and nutritional factors relating to such growth. Eleven papers, each representing some current study in these fields of oncology, comprise this volume. The results obtained are conservatively evaluated.

Albert Tannenbaum observed that simple underfeeding inhibited the formation of tumors in mice. This was because of caloric restriction rather than the absence of some specific food component. Furthermore, in a study of cutaneous cancer induced by 3:4 benzpyrene, tumors developed in only 11 mice of 50 on a restricted diet. Among 50 mice fed ad libitum 32 showed tumors. Data are presented demonstrating that 8 different types of mouse tumors and leukemia are inhibited by caloric restriction. Indirect "restriction" in caloric intake accomplished by feeding sodium fluoride with resulting anorexia and keeping mice in the cold also diminished the frequency of cancer.

Investigations by J. A. Miller were directed toward (1) the development of a satisfactory purified diet for the production of hepatic tumors in the rat by feeding azo dye and (2) an assay procedure for evaluating the effects produced by changes in this diet. Miller studied the carcinogenicity of several azo dyes and considered that when *P*-dimethylaminoazobenzene is fed in various diets the riboflavin level in the liver of the rat is an important factor in determining the probability that a given liver will develop a tumor.

The addition of liver and yeast to a brown rice diet produced some protective effect in J. C. Kensler's studies. A riboflavin supplement in the presence of adequate protein increased the resistance of the rat to hepatic damage and tumefaction by N, N-dimethyl-*P*-aminoazobenzene (DMB). Experiments with casein suggested that, although the methionine content of casein was important for protection, other factors in the casein are probably also necessary for maximum effect. There is a stage in the hepatic tumors produced by DMB at which, if the feeding of the dye is stopped and dried milk or yeast is added, the outcome can be altered. Evidence neither proved nor disproved that azo dyes, and perhaps

other carcinogens, damage cells and produce tumors by directly or indirectly inactivating certain cellular enzymes, producing an "induced or conditioned deficiency."

The effect of diets low in cystine, lysine and tryptophane on the incidence of induced leukemia was investigated by J. White, F. R. White and G. B. Mider. Growth of young mice was prohibited by restriction of amino acid but indefinite maintenance was possible. No significance in the incidence of leukemia was observed among mice fed on diets restricted in lysine or tryptophane. Those fed restricted cystine diets showed a reduction in leukemia from 92.1 per cent in the controls of 55 per cent in the animals studied.

R. Engel, D. Copeland and W. D. Salmon reported that prolonged feeding of diets deficient in choline resulted in occurrence of neoplasms in one or more sites—bronchi, liver, subcutaneous tissues, pancreas and bladder—in 14 of 18 rats.

Certain characteristics of the mammary tumor milk agent were briefly summarized by J. J. Bittner. It is present and active in the thymus, spleen, lactating mammary tissue, spontaneous mammary cancer, liver and whole blood. It becomes inactive at pasteurization temperature within thirty minutes but remains active after filtration through Seitz and Berkefeld filters or treatment with glycerine and desiccation. If cell-free filtrates are injected into chick embryos, the agent may be recovered from filtered or unfiltered yolk. Animals of susceptible stocks become resistant to the agent with increasing age, but this resistance is overcome by repeated injections. Bittner concluded that the small size of the agent, its ability to propagate in the living cell and its antigenic properties classify it as an infectious agent or virus.

W. J. Robbins pointed out that, while cancer is a disease of animals rather than plants, the problem of growth is common to all living tissue. Mutations and autonomous tumors of plants are discussed.

E. L. Tatum reviewed the evidences of his own experiments, as well as many others which are compatible with the mutational theory of cancer. Although a critical evaluation of the evidence cannot as yet be made, there are known facts regarding the changes occurring during carcinogenesis which seem to support the theory.

G. W. Kidder studied certain aspects of the nutrition of a monocellular organism, the Tetrohymena geleii, by using an amino acid mixture composed of the ten essential amino acids with serine added. The life of the culture was curtailed. When ammonium pyruvate and dextrose were supplemented, increasing the caloric content of the medium, the shape of the growth curve was normal and a fairly high population was maintained for long periods of time. He suggested exploration of the possibility that part of the nitrogen requirement of the human body may be supplied by ammonium salts.

P. R. White emphasized the difficulty of studying normal tissues in vitro precisely. However, the knowledge of vitamin and hormone requirements in nutrients has increased the possibilities of study of tissue cultures. White used a wholly synthetic nutrient composed of inorganic factors and vitamins and reported it possible to maintain the beating of chick embryo heart muscle for six weeks and other tissues for approximately the same period. He subsequently advanced the possibility that mutations, many of which are unrecognizable—although some such as alkaptonuria and albinism are evident—are occurring constantly in the body.

H. P. Morris considered it reasonable to believe, although difficult to evaluate, that certain dietary constituents, including vitamins, are involved in the

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genesis or growth of tumors. Studies were conducted to determine the influence of vitamin intake (1) on the in vivo growth of tumors already formed and (2) on the genesis of cancer, using spontaneous mammary mouse tumor for the investigation. Among his observations, he reported that extreme deficiencies of pantothenic acid and riboflavin if produced in a short period of time rapidly decreased the rate of growth of the cancer. Similar reduction in pyridoxine did not affect the rate of growth. The average rate of growth of the mammary tumors was depressed in the presence of added thiamine intake.

The publication is illustrated; there is an extensive bibliography, and the reports should prove of interest to students of growth and nutrition, as well as those concerned with neoplasms.

Congenital Malformations of the Heart. By Helen B. Taussig, M.D. Price, $10. Pp. 618, with illustrations. New York: Commonwealth Fund, Division of Publications, 1947.

There has long been a need for an authoritative textbook presenting the clinical manifestations of congenital cardiac malformations. The recent spectacular advance in surgical treatment of cardiovascular anomalies has intensified that need. It has been admirably met in Dr. Taussig's present volume.

The book is divided into four parts. The first section deals with the physiology of the malformed heart and discusses diagnostic principles. The second considers those malformations which deprive the body of an adequate amount of oxygenated blood. The third part is devoted to malformations which permit the body to receive an oxygen supply sufficient to meet the needs of the person. The last part is given over to treatment.

A definite pattern is followed in the discussion of each malformation. The nature of the malformation is first explained, then the course of the circulation is outlined, both during fetal life and after the circulation to the lungs has been established. The clinical findings, the cardiac findings, the results of roentgenographic and fluoroscopic studies and the electrocardiographic observations follow. Three color diagrams show the course of the circulation in each of the malformations. The drawings of the contours of the abnormal hearts, with the drawings of normal hearts juxtaposed, give one a vivid idea of the effect produced on the heart by the malformation under discussion.

The book has been written chiefly from the author's extensive personal experience with a large number of patients and her study of a great amount of pathologic material. On this account she has not undertaken an extensive bibliography. As one reads the book, one is impressed by the simplicity and clarity of presentatiton and realizes that these stem from the author's profound knowledge of the subject.

This work will prove a boon to every student of congenital cardiovascular anomalies and will be especially welcomed in those clinics which are undertaking to perform the Blalock-Taussig operation, or a modification of it, for the relief of congenital pulmonary stenosis. Accurate diagnosis must precede successful surgical treatment.

In the foreword, Dr. Edwards A. Park states: "Dr. Taussig has done for the clinician what Maude Abbott did for the pathologist." That is high praise. All who are familiar with the subject of congenital heart disease will agree that it is well merited.

Headache. By Louis G. Moench, M.D., Assistant Clinical Professor of Medicine, University of Utah School of Medicine. Price, $3.50. Pp. 207, with 58 illustrations. Chicago: The Year Book Publishers, Inc., 1947.

Although headache is the most frequent symptom of complaint encountered in general medical practice, there is an extraordinary lack of comprehension regarding the numerous distinct and definite groups into which the malady correctly falls, as well as which structures are sensitive or insensitive to pain and whence such pain derives. Consequently there is ignorance as to the source, presumable cause and therapy in groups or individual cases.

In this volume Dr. Moench has given an admirable, clearcut and readily understandable presentation of the subject. Beginning with a chapter on the pathologic anatomy and physiologic mechanism of headache, he lists those structures, particularly blood vessels and nerves, which are sensitive to pain, and describes the hemodynamic factors, their causes, effects and eventual localization, responsible for particular symptoms.

In subsequent chapters, headache from organic sources such as cerebral tumor, spinal puncture, trauma and other intracranial pathologic lesions, as well as that arising from ocular and nasal disorders, and from the neck, is discussed.

Neuralgias mediated by cranial nerves, while usually felt more as pain than as headache, are given careful consideration, particularly the syndromes of sphenopalatine and vidian neuralgia. Headache as a manifestation of numerous systemic and toxic disorders is difficult to distinguish from that of emotional and psychogenic origin, thus requiring a most comprehensive investigation before a functional basis is predicated. When due to actual systemic disease, the headache is most frequently caused by distortion of a pain-sensitive structure by alteration of normal arteriovenous relationship.

The chapters covering histamine headache (Horton's cephalalgia) and migraine, which should probably be classified as a disorder of histamine tolerance, indicate by the extensive discussion of etiology, types and therapy how little general agreement there is on the subject. The author, however, when speaking of histamine desensitization, uses a term which is ambiguous and frequently leads to confusion. Histamine, decarboxylated histidine, is nonantigenic, hence can produce neither antibodies nor allergic or anaphylactic reactions on subsequent exposures to it. Therapy consists, not in a process of desensitization, as in the allergic sense, but in the production of increased tolerance, as in the case of alcohol, tobacco and numerous drugs, presumably the stimulation of histaminase formation.

The majority of physicians are not particularly conversant with psychosomatic problems, and the final chapter on headache of emotional origin gives the author's views on compensation, since the psychoneurotic person who is able to achieve a psychologic compromise, such as headache, unpleasant as it may be, may continue to live in the world of reality, whereas the psychotic patient, abandoning the struggle, may find it unnecessary, or find himself unable, to convert his conflicts into physical symptoms.

The material on the vasodilatation headache of Wolff, important because of its frequency, its common confusion with other types and the general lack of recognition and understanding of the mechanism of its production, as well as of the therapeutic results, temporary by infiltration with local anesthetic (eucupine) and permanent by ligation and division of the artery, would suggest necessity for further amplification of this phase of headache.

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Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Bornehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associacao Paulista de Medicina, Seccao de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjorup, Dronning Louises Bornehospital, Copenhagen.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p.m.

Schweizerische Gesellschaft fur Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela Deheza, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

Sociedad Mexicana de Pediatria

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

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SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., Second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez Cèsar, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre, Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÈTÈ DE PÈDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7°, France.
Secretary: Dr Maurice Lamy, 94 rue de Varenne, Paris 7°, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenda Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

American Academy of Pediatrics

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlanta, Ga. Time: April 13-15, 1949.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

American Hospital Association, Massachussetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

Canadian Society for the Study of Diseases of Children

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

Society for Pediatric Research

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Wm. D. Rothwell, Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel, Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949.

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Arizona Pediatric Society

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

Arkansas State Pediatric Association

Chairman: Dr C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

Louisiana State Pediatric Society

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

Medical Society of the State of New York, Pediatric Section

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Jersey Medical Society, Pediatric Section

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3516 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

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LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Walter R. Coles, 604—2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granda Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Forth Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Forth Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders, Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

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Pittsburgh Pediatric Society

President: Dr. J. A. Gilmartin, 3708-15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

Queens Pediatric Society

Chairman: Dr. Walter C. A., Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

Waco Pediatric Society

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).